The impact of chlorine substituents on the regioselectivity of Pd(0)-catalyzed direct arylation of heteroaromatics.

Ivan Petrov

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Supervisors: Dr. Keith Fagnou, Dr. Robert Ben

Department of Chemistry
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Dedicated to the memory of Keith.

This work is a part of his legacy.

ACKNOWLEDGEMENTS

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ABSTRACT

The regioselectivity in Pd(0)-catalyzed direct arylation of pyrrole, thiophene, and indole can be improved by blocking some of the reactive sites with a chloride group, leading to increased yields of the desired regioisomers. Competition experiments and computational studies show that the blocking group also activates the substrates toward arylation. Due to the activated nature of chlorinated heteroaromatics, rare and sought after regioisomers, such as 3-arylthiophenes, can be obtained under mild conditions in good yields. Chlorine-bearing thiophenes arylated at C3 and C4 have the potential to undergo controlled regioregular polymerization under conditions developed in the field of polythiophene chemistry. Mechanistic studies support the hypothesis that the arylation of the substrates under investigation likely proceeds *via* the CMD transition state.

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LIST OF SYMBOLS AND ABBREVIATIONS

Bn - benzyl

^{i}Bu - iso-butyl

^{t}Bu - tert-butyl

n-BuLi - *n*-butyllithium

n-Bu - *n*-butyl

CMD - concerted metalation-deprotonation

Cy - cyclohexyl

dba - dibenzylidene acetone

DFT- density functional theory

DMA - *N,N*-dimethylacetamide

DMF - *N,N*-dimethylformamide

DMSO - dimethylsulfoxide

DPPF - 1,1'-bis(diphenylphosphino)ferrocene

ΔE - activation energy

ΔE_{Dist} - distortion energy

$\Delta \mathrm{E}_{\mathrm{Int}}$ - interaction energy

ΔE_{PA} - proton affinity

$\mathrm{Et_3N}$ - triethylamine

EWG - electron-withdrawing group

ΔG - Gibb`s free energy of activation

HMDS - hexamethyldisilazane

HOMO - highest occupied molecular orbital

HT - ``head-to-tail`` polythiophene

KIE - kinetic isotope effect

L - ligand

LUMO - lowest unoccupied molecular orbital

NMR - nuclear magnetic resonance

OAc - acetate

Ph - phenyl

PPh_3 - triphenylphosphine

^{i}Pr - iso-propyl

RE - reductive elimination

S_EAr - electrophilic aromatic substitiution

S_E3 - single-step electrophilic aromatic substitiution

THF - tetrahydrofuran

TMEDA - tetramethylethylenediamine

Ts - tosyl

TS - transition state

X - halide

η - hapticity of ligand

1. INTRODUCTION

1.1 General

The heterobiaryl motif is prominent among a great variety of synthetic organic molecules and natural products, spanning a wide range of applications from pharmaceuticals to materials science[1,29,54]. Transition metal-catalyzed cross-coupling reactions have become the most conventional among carbon-carbon bond forming reactions for (hetero)arenes[2]. For palladium-catalyzed processes, pre-activation of both coupling partners, a critical step of these traditional protocols, requires substrate derivatization to yield the corresponding organometallic species. Direct arylation via C-H bond activation offers an attractive environmentally benign alternative to Suzuki-Miyaura or Stille couplings. An unactivated (hetero)arene can be coupled with an aryl (pseudo)halide, forming acid (HX) as a by-product (Figure 1)[1,2,3,4].

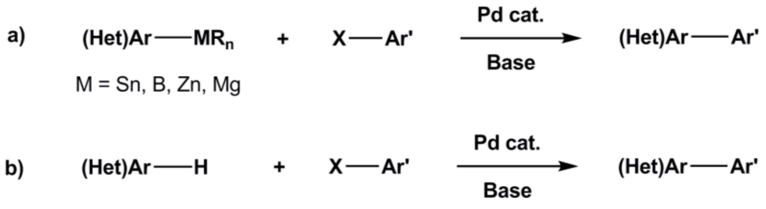
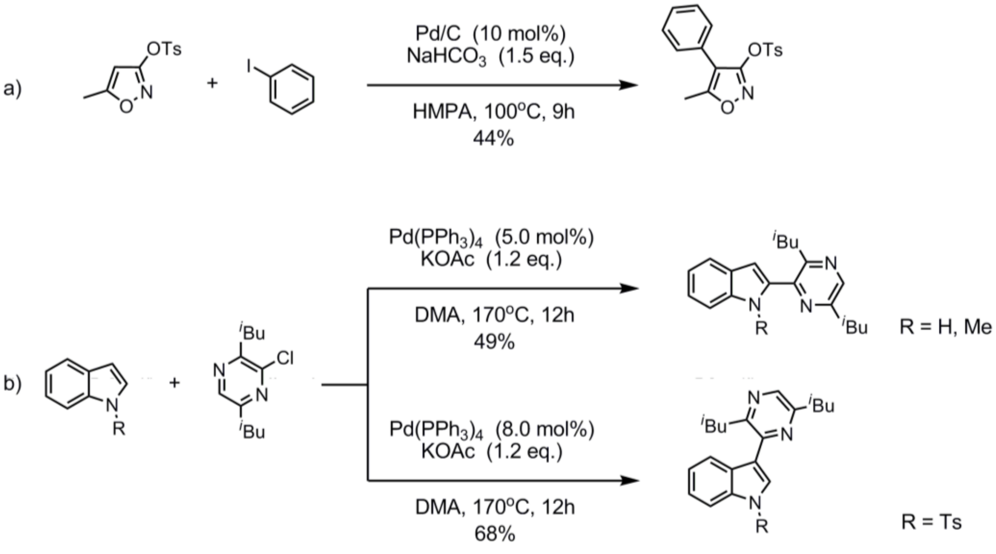


Figure 1. Conventional cross-coupling (a) versus direct arylation (b) of (hetero)arenes.

The first report of an intermolecular Pd(0)-catalyzed direct arylation of heteroaromatics came from Tajima and co-workers in 1982[5]. They described a procedure for arylating 3,5-disubstituted isoxazoles with aryl iodides in the presence of a heterogeneous palladium catalyst. Three years later Ohta published his results for the first homogeneous Pd(0)-catalyzed direct arylation[6]. Free (NH) and N-substituted indoles were coupled with chloropyrazines to give C2 and C3 arylated products (Scheme 1).



Scheme 1. Pioneering work on direct arylation of heteroarenes by Tajima (a) and Ohta (b).

Currently, as the field of direct arylation of heteroaromatics continues to evolve, one particular challenge demands special attention from researchers - regioselectivity of arylation. Due to their electronic structure, heteroarenes possess an inherent bias in site selectivity under direct arylation conditions (Figure 2)[4]. Enhancing the reactivity at certain positions or diverting it from other sites has become an important factor in the development of high-yielding direct arylation protocols.

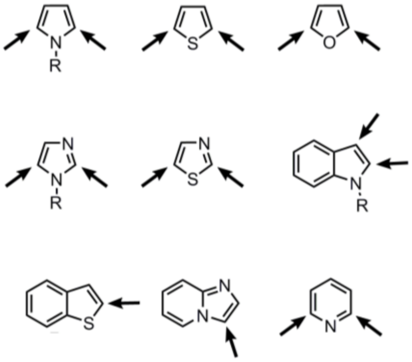
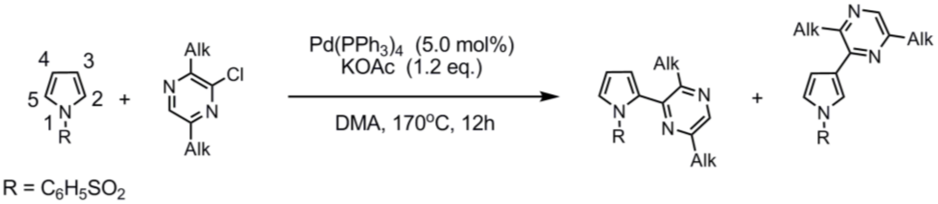


Figure 2. Most favourable sites (arrows) for direct arylation of several heteroarenes.

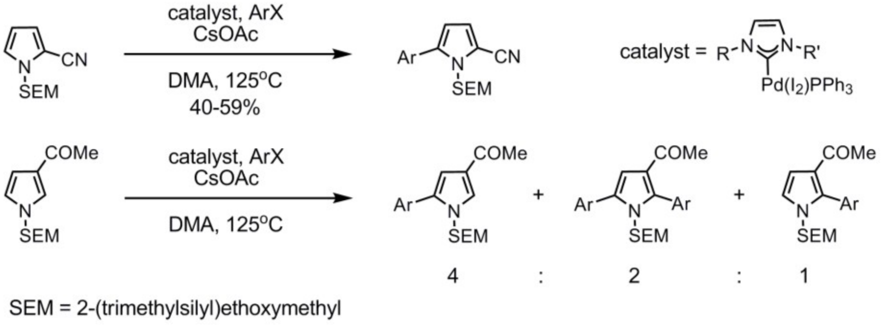
1.2 C2 or C5 monoarylated pyrrole and thiophene

Each ring atom of pyrrole carries electron density, whose value is greater than one. This makes the heterocycle π-excessive; its aromaticity is intermediate between that of furan and thiophene[7]. Under direct arylation conditions unsubstituted pyrrole reacts at C2 and C5. Early reports of C2 arylated pyrroles came from the group of Ohta, who initially used chloropyrazines as coupling partners and $Pd(PPh_3)_4$ as a catalyst to obtain the products in low yields due to the formation of undesirable C3 arylated producs (C2:C3 from 1:1 to 2:5) (Scheme 2)[6]. The methodology was later improved to allow high-yielding reactions of other aryl chlorides with N-zincated pyrrole derivatives with the aid of the JohnPhos ligand[8].



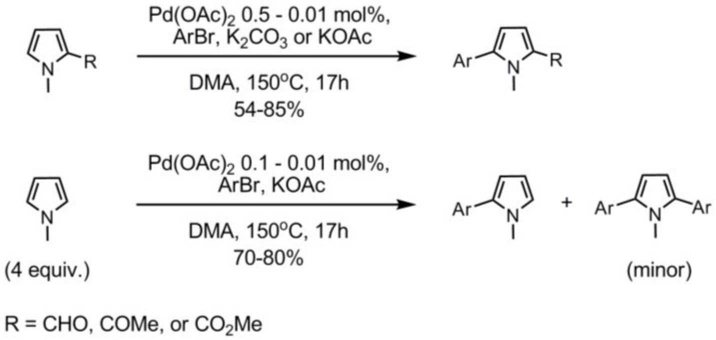
Scheme 2. Ohta's direct arylation of pyrrole with chloropyrazines

More recently, Sames utilized 2-(trimethylsilyl)ethoxymethyl (SEM) protected pyrroles in reactions catalyzed by palladium imidazolyl carbene comlexes[9]. In order to avoid the formation of C2,C5 diarylated side-products the C2 position of the pyrroles was blocked with a cyano group. In the case where a C3 substituted pyrrole was used, the authors reported a 4:2:1 ratio of C5 arylated:C2,C5 diarylated:C2 arylated products (Scheme 3). The products, obtained in moderate yields, could be subsequently deprotected through the cleavage of the SEM group.



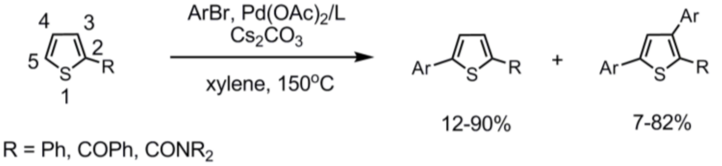
Scheme 3. Sames' direct arylation of 2 and 3-substituted pyrroles.

Sadighi and co-workers reported the use of pyrrole anions to generate N-zincated species *in situ*; these substrates could then undergo C2 arylation with aryl halides in the presence of catalytic Pd(OAc)$_2$ or Pd$_2$(dba)$_3$ along with sterically demanding 2-(dialkylphosphino)biphenyl ligands[10]. With this methodology stoichiometric amounts of metal salts were generated as by-products. The group of Doucet disclosed a method for direct arylation of 2-substituted N-methyl pyrroles with various aryl bromides[11]. Under phosphine-free conditions, in the presence of a carbonate base, and catalyzed by Pd(OAc)$_2$ the process, which required a high temperature (minimum 150°C), afforded monoarylated products in good to excellent yields. In cases where the reactive C2 position of the pyrrole was not blocked with an aldehyde or acetyl group, a large excess (4 equivalents) of the pyrrole was needed to suppress C2, C5 diarylation (Scheme 4).



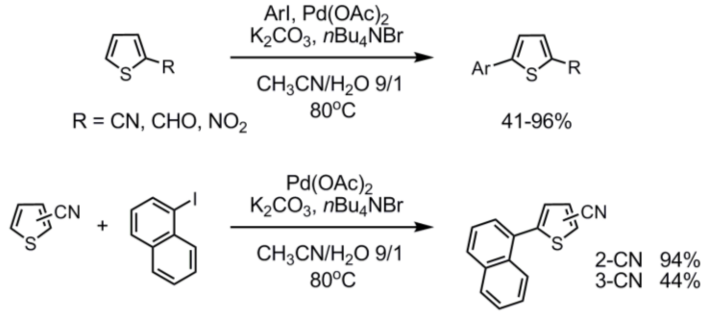
Scheme 4. Doucet's ligandless direct arylation of pyrroles.

Like pyrrole, thiophene is a π-excessive heteroarene. It is more aromatic than both furan and pyrrole possibly because the lower elecronegativity of sulfur allows its lone pairs to be more effectively incorporated into the conjugated system, alternatively, the ability of sulfur to expand its octet can lead to the inclusion of the 3d orbitals into the π-system[7]. Similarly to pyrrole, when subjected to direct arylation, unsubstituted thiophene reacts at C2 and C5. Using the same methodology as he applied to pyrroles, Ohta reported the preparation of some of the first arylthiophenes over two decades ago[6]. Since then the interest in this class of compounds has increased significantly in the pharmaceutical sector due to thiophene's potential role as a versatile isostere for benzene[4]. Thiophene-based materials have been also gaining recognition for their useful and highly tuneable properties[29]. Miura reported a method for thiophene direct arylation with aryl bromides in the presence of $Pd(OAc)_2$, the Buchwald's ligand ($P(o\text{-biphenyl})(^t Bu)_2$) or $P(^t Bu)_3$, and a carbonate base[12]. The reactive C2 position was blocked in order to maximize the yields of the monoarylated products. The authors also mentioned that the use of excess aryl bromide led to selective C5, C3 diarylation (Scheme 5).



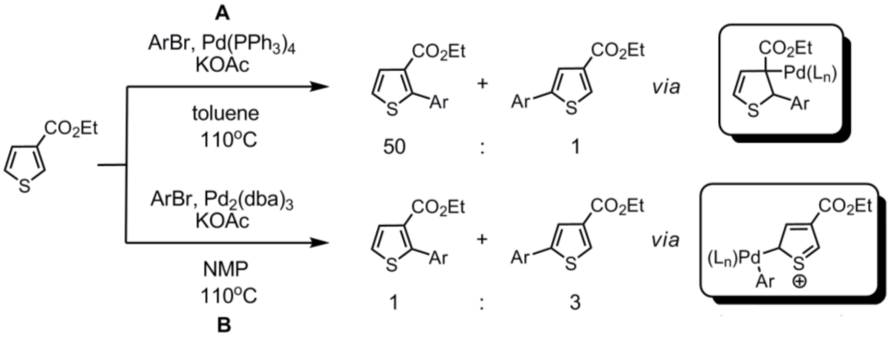
Scheme 5. Miura's direct arylation of 2-substituted thiophenes.

Lemaire and co-workers disclosed a significantly milder set of conditions with $n Bu_4NBr$ as an additional base, which were unfortunately limited to aryl iodides[13]. Once again, the thiophene substrates were substituted at C2 to avoid unwanted diarylation, which was observed with several thiophenes bearing a C3 substituent or none at all (Scheme 6).



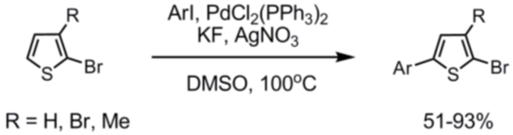
Scheme 6. Lemaire's direct arylation of 2-substituted thiophenes.

Sharp developed a method for direct arylation of 3-esterified thiophene where the regioselectivity of the process could be controlled to some extent by altering the reaction conditions[14]. According to the authors, the use of stabilizing phosphine ligands and a non-polar solvent (Conditions A) favoured Heck-type carbopalladation with a stabilized σ-bonded Pd(II) intermediate, which could collapse to yield the C2-arylated product. Conversely, a lack of supporting ligands and the presence of a polar solvent (Conditions B) promoted ionization of the Pd-X to form an electrophilic species prone to reacting at the most electron-rich C5 position of the 3-esterified thiophene (Scheme 7).



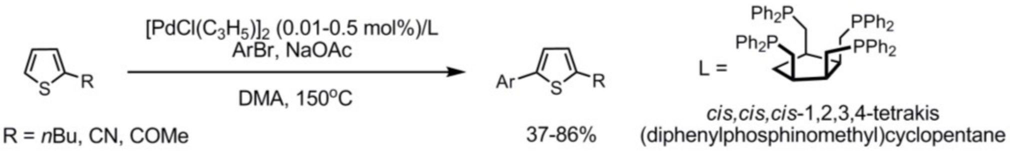
Scheme 7. Regioselective arylation of thiophene by Sharp.

Mori and co-workers investigated $PdCl_2(PPh_3)_2$-catalyzed direct arylation of C2-brominated thiophene with $AgNO_3$ as an additive[15]. The procedure, limited to aryl iodides, allowed the carbon-bromine bond of the C5-arylated products to be preserved for further elaboration of the carbon skeleton via conventional cross-coupling (Scheme 8).



Scheme 8. Mori's direct arylarion of brominated thiophene.

Doucet and co-workers proposed the use of an unconventional multidentate ligand to achieve efficient catalysis under strictly anhydrous conditions at low catalyst loadings[16]. Yet again, monoarylation was secured through the use of a blocking group at C2 of thiophene. Electron-deficient thiophenes were reported to be less reactive than electron-neutral ones (Scheme 9).

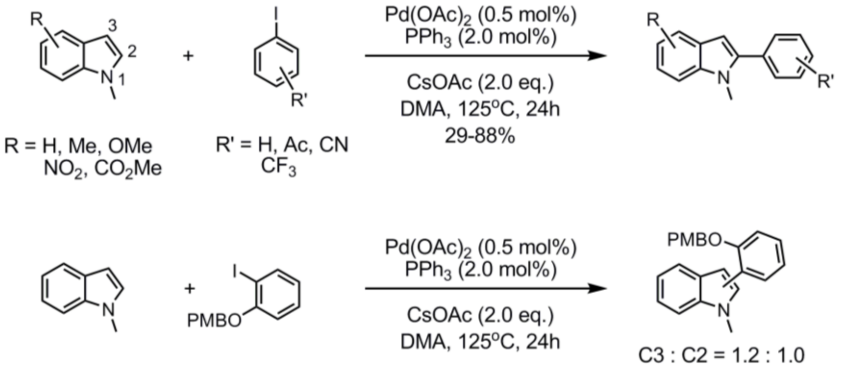


Scheme 9. Doucet's arylation of thiophene using a multidentate ligand.

The same group later reported a ligand-free procedure carried out at high temperatures (150°C) with $Pd(OAc)_2$ as the catalyst[17]. Similar 2-substituted thiophene derivatives were used as substrates in most cases; several examples of unsubstituted thiophene arylation were given where thiophene was used in a large excess (5 equivalents) to suppress diarylation.

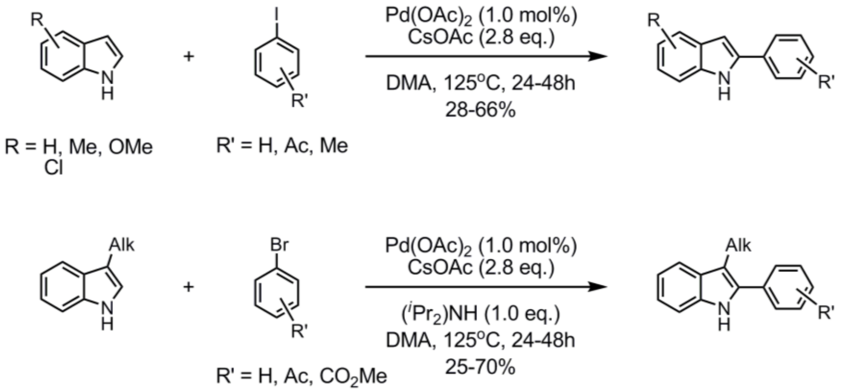
1.3 C2 or C3 monoarylated indole

Benzo[*b*]pyrrole also known as indole is less reactive than pyrrole. Direct arylation takes place at C2 and C3, largely depending on reaction conditions as well as the electronic and steric properties of the indolic substrate. The greatest HOMO coefficient resides on C3; electrophilic substitution at this position is most favourable proceeding *via* an iminium σ-complex[7]. Indole was among the first heterocycles to be submitted to the direct arylation protocols developed by Ohta and co-workers (Scheme 1b)[6,18]. The C2 products were obtained in moderate to good yields using free (NH) or N-alkyl indoles as substrates in combination with $Pd(PPh_3)_4$ and KOAc. The use of   N-benzyl and N-tosyl indole led to very low yields of the desired products. In 2004 the group of Sames described a procedure for the direct C2 arylation of N-methyl indole with aryl iodides. Only 0.5 mol% of the $Pd(OAc)_2$ catalyst and 2.0 mol% of PPh_3 was required to form the products in good yields[19]. The authors commented on the fact that the use of bulky haloarenes, especially, *ortho*-substituted ones was detrimental to the regioselectivity of the reaction, resulting in C2/C3 product mixtures (Scheme 10).



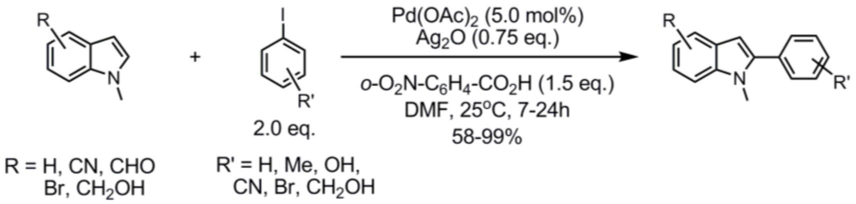
Scheme 10. C2 arylation of N-methyl indole by Sames.

In 2008 Bhanage and co-workers achieved C2 arylation of N-methyl indole by using their own catalyst Pd(TMHD)$_2$ (TMHD=2,2,6,6-tetramethyl-3,5-heptanedionate), developed as an alternative to phosphine ligands, albeit at high loadings (10 mol%)[20]. An entirely phosphine-free method applicable to free (NH) indoles was published by Sames; Pd(OAc)$_2$ and CsOAc in DMA at 125°C were used in combination with aryl iodides to yield the C2 arylated indoles[21]. The protocol was initially incompatible with aryl bromides, but the use of 3-alkyl indoles to block the reactive C3 position and stoichiometric (^{i}Pr$_2$)NH resulted in moderate to good yields of the products (Scheme 11).



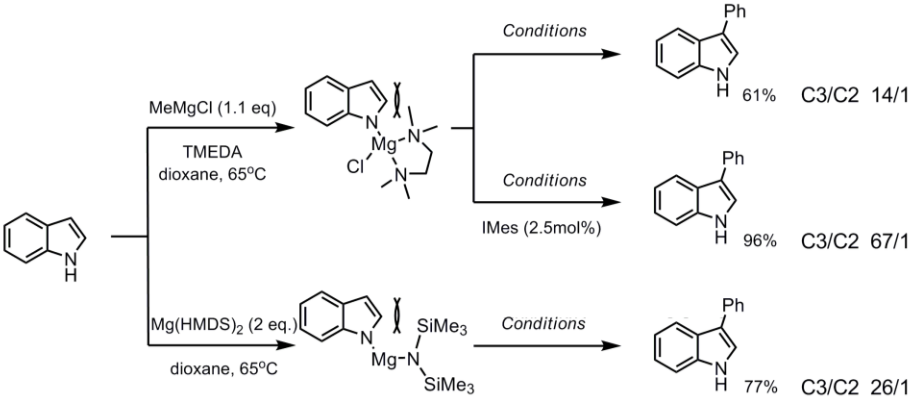
Scheme 11. Sames' direct C2 arylation of free (NH) indoles.

In 2008 Larossa and co-workers disclosed a room-temperature and phosphine-free procedure for the direct C2 arylation of N-methyl indole, which was, unfortunately, limited to aryl iodides[22]. By employing Ag$_2$O as a base together with a slight excess of *o*-nitrobenzoic acid in DMF the authors were able to obtain good to excellent yields of the desired products; substitutions on both the haloarene and the indole were well tolerated (Scheme 12).



Scheme 12. Larossa's direct C2 arylation of N-methyl indole.

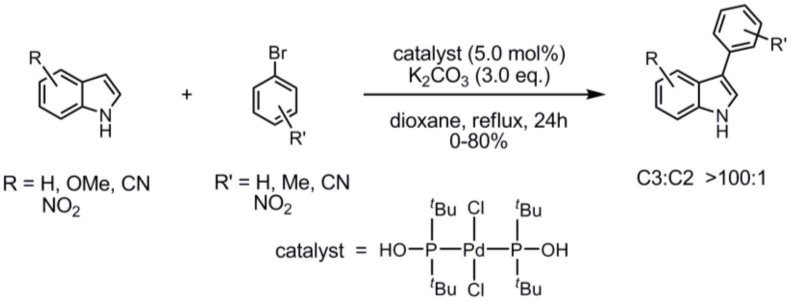
During his studies of direct arylation of indole Ohta reported that tosyl and benzyl nitrogen protecting groups promoted the formation of C3 arylated products (Scheme 1b)[6]. The authors also noted that chloropyrazine coupling partners bearing bulky groups, such as ^{i}Pr and ^{i}Bu favoured arylation at C3 with C3:C2 products ratios of 50:1. The work of Sames validated these early results when the group published their findings concerning the influence of haloarene bulk on C2/C3 selectivity of N-methyl indole direct arylation (Scheme 10). As a development of the concept of selective C3 arylation of indole through steric congestion of C2, Sames and co-workers were able to use N-Mg salts of free (NH) indole with sterically demanding TMEDA or HMDS groups as well as the bulky IMes ligand on the catalyst to force the arylation process to take place at C3 (Scheme 13)[23].



Conditions: Pd(OAc)$_2$ (2.5mol%), PPh$_3$ (10mol%), CsOAc (2 eq.), PhI, dioxane,125 °C, 24h

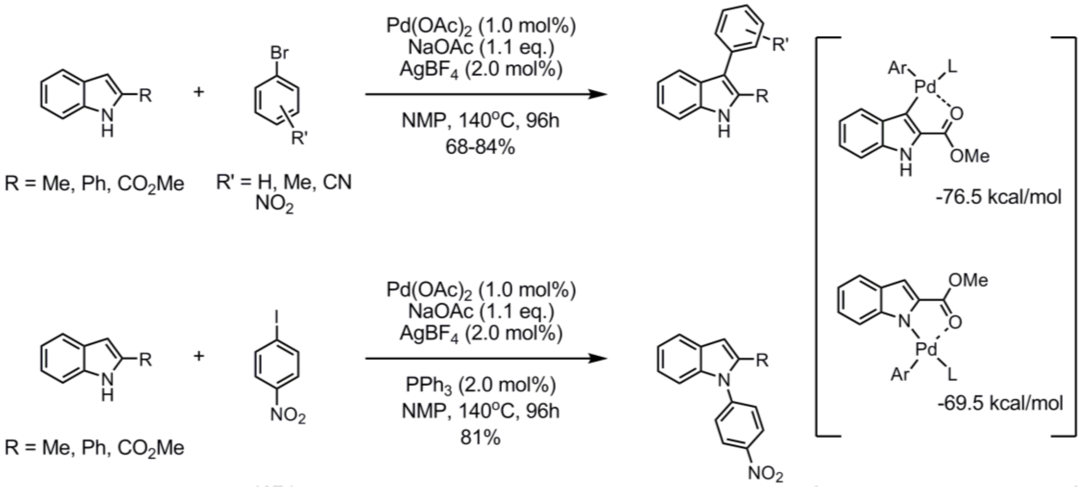
Scheme 13. Sames' direct C3 arylation of indole N-Mg salts.

Capitalizing on the steric bias of the reaction, Lemaire and co-workers used sterically congested *p*-bromo-*m*-nitroanisole to arylate N-methyl indole in a conventional $Pd(OAc)_2/PPh_3$ catalyzed procedure and observed a modest 4:1 C3:C2 regioselectivity[24]. In 2007 Zhang and co-workers developed a highly regioselective method for direct C3 arylation of free (NH) indole with aryl bromides using an air-stable bulky Pd-phosphinous acid (POPd) comlex as a catalyst[25] . The authors were able to obtain the products in moderate to good yields with exceptional >100:1 C3:C2 selectivity. The drawbacks of the method include the high cost of the catalyst and the lack of reactivity observed with indoles bearing electron-withdrawing groups (Scheme 14).



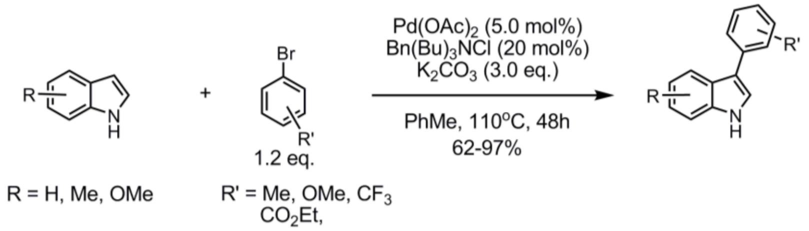
Scheme 14. Indole C3 arylation using a Pd-phosphinous acid catalyst.

Djakovitch and co-workers described a procedure where a series of free (NH) indoles were arylated at C3 with bromoarenes in the presence of $Pd(OAc)_2$, NaOAc, and catalytic $AgBF_4$[26]. The reaction was diverted from C2 by blocking it with an alkyl or aryl group. Interestingly, the use of iodoarenes and PPh_3 resulted in N-arylation of the indole substrates. At the same time, regardless of the nature of the aryl halide, only C3 arylation occured when the C2 blocking group was a carboxylate moiety, presumably due to the greater stability of the proposed TS (Scheme 15).



Scheme 15. C3 arylation of C2-substituted indoles by Djakovitch.

Recently, Bellina and co-workers reported a free (NH) indole arylation protocol where $Pd(OAc)_2$, K_2CO_3, and a quaternary ammonium salt (the combination of reagents known as Jeffery conditions[27]) were used to improve the C3 regioselectivity of an older procedure[28]. Originally, the reactions took place in the presence of phosphine ligands and produced mixtures of C3, C2, and N-arylated products. The use of ammonium salts such as $Bn(Bu_3)NCl$, which supposedly stabilize soluble Pd clusters preventing the formation of catalytically inert Pd black, resulted in nearly complete C3 *versus* C2/N1 selectivity with good to excellent yields. The procedure was, however, not applicable to N-alkylated indoles and bromoarenes bearing strongly electron-withdrawing substituents (e.g. 4-bromonitrobenzene) (Scheme 16).



Scheme 16. Bellina's C3 arylation of free (NH) indole using Jeffery conditions.

1.4 C3 or C4 monoarylated thiophene

Unsubstituted thiophene does not undergo direct arylation at C3 and C4[4]. Despite this fact, direct arylation strategies to obtain these uncommon derivatives exist and are particularly useful in the field of polythiophene materials (Figure 3)[4,29]. Thiophene arylated at C3 has been successfully used as a monomer in the construction of wide-bandgap organic electrodes for elecrtochemical capacitors[30]. The possibilty of changing the substituents present on the aryl moiety confers the property of tunability on the polythiophene electrode. Direct arylation has the potential to facilitate the syntheses of series of C3 arylated thiophene analogues required for optimization studies. Thiophene derivatives monoarylated at C3 as well as diarylated at C3 and C4 have found applications in the field of organic light emitting diodes (OLEDs)[31]. Once again, the ability to vary the aryl groups in order to fine-tune the emmission wavelength of a given polymer plays a critical role in the development of these materials.

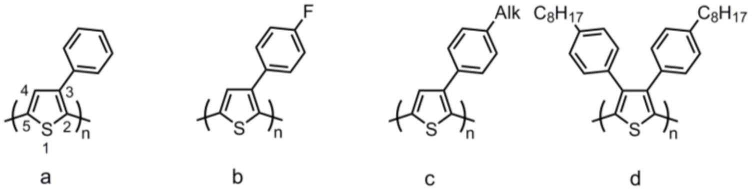
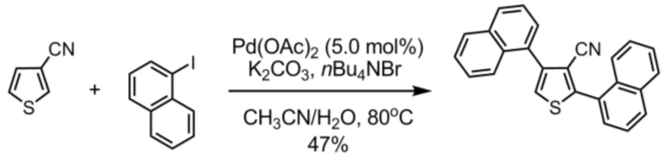


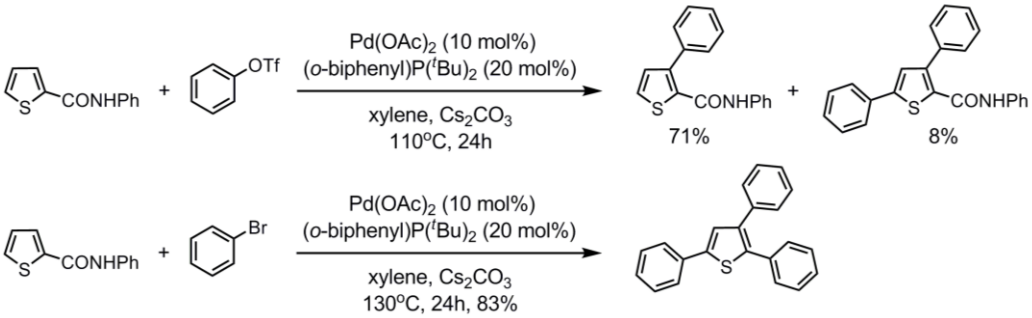
Figure 3. Polythiophene-based organic electrodes (a,b) and OLEDs (c,d).

Over a decade ago Lemaire and co-workers described an intriguing result in the course of their studies on thiophene direct arylation[32]. Upon treatment of 3-cyanothiophene with 1-iodonapthalene in the presence of $Pd(OAc)_2$ and $n$$Bu_4NBr$ they were able to obtain the 2,4-diarylated product in modest yield with no by-products (Scheme 17). The unexpected lack of reactivity at C5 was attributed to the activation of the normally inert C4 position by the proximal cyano group.



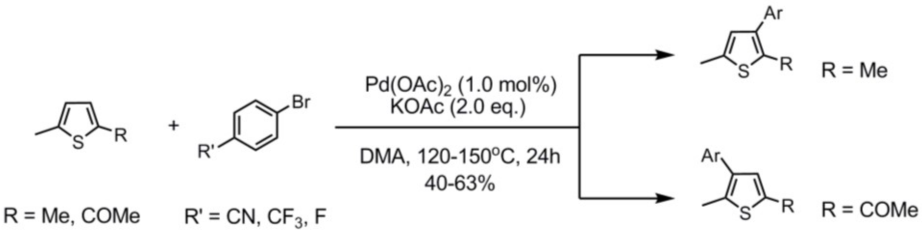
Scheme 17. Lemaire's C2, C4-diarylation of 3-cyanothiophene.

Similarly, by employing a potentially activating C2 amide group in a conventional protocol utilising Pd(0) and a phosphine ligand, the group of Miura demonstrated that mono-, di-, and tri-arylated products can be obtained from 2-thiophenecarboxamides[33]. At high temperatures the products were shown to undergo decarbamoylation rendering the C2 position available for arylation (Scheme 18).



Scheme 18. Miura's multiple arylation of 2-substituted thiophene *via* decarbamoylation.

The initial C3 arylation was thought to proceed by a coordination-assisted mechanism with the aid of the carbonyl oxygen at C2, but subsequent reactions at C5 and C2 were deemed electrophilic. Recently, the same group reported a full per-arylation of 3-thiophene carboxylic acid under harsh conditions (170°C) *via* three C-H bond cleavage events, followed by decarboxylation[34]. Doucet and co-workers found that by blocking the most reactive positions on the thiophene skeleton, direct arylation can be forced towards C3 and C4[35]. Thus, they disclosed a method by which 2,5-disubstituted thiophenes can be arylated with *para*-substituted bromoarenes in the absence of a phosphine ligand. Symmetrical 2,5-dimethyl thiophene underwent C3 arylation, however, 2-acetyl, 5-methyl thiophene was arylated exclusively at C4 (Scheme 19). The products were obtained in good yields, but the drawbacks of this methodology include a high reaction temperature (120-150°C) and low tolerance for electron-rich bromoarenes .



Scheme 19. Doucet's C3 and C4 arylation of 2,5-disubstituted thiophenes.

1.5 Mechanistic details of Pd(0)-catalyzed direct arylation of (hetero)arenes.

Several theories have been proposed concerning the mechanism of direct arylation (Figure 4)[2,3]. The field has been subject to controversy for many years and to date the only point of consensus among researchers is that no single mechanism can account for the range of experimental outcomes observed in the field of transition-metal catalyzed (hetero)arene direct arylation[1] . In fact, some experts propose that a number of mechanisms, all leading to the same outcome, can be operative in a reaction depending on the reaction conditions (i.e. the choice of solvent, ligand, or Pd source) and the nature of the substituents present on the coupling partners[18]. Early research strongly favoured the electrophilic aromatic substitution pathway (S_EAr). In particular, a study of indolizine arylation carried out by the group of Gevorgyan led the researchers to conclude that an electrophilic mechanism could account for the observed results[36]. In the indolizine substrate class both the unsubstituted and the 2-substituted forms were found to undergo direct arylation exclusively at C3 under standard conditions. In order to elucidate the mechanism of this transformation the group conducted a series of experiments,

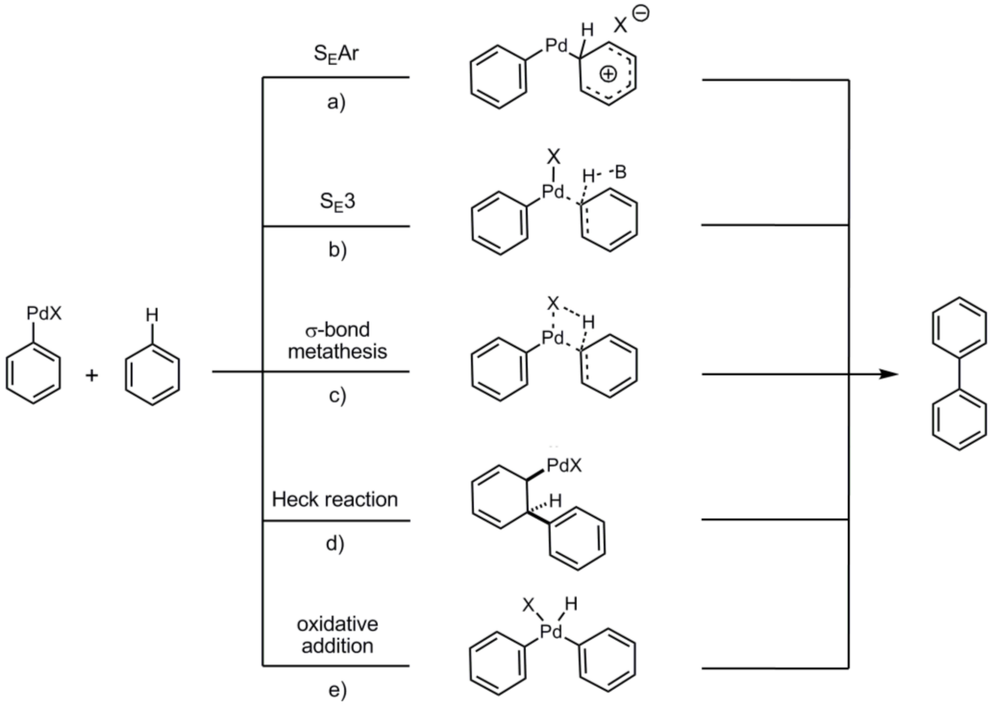
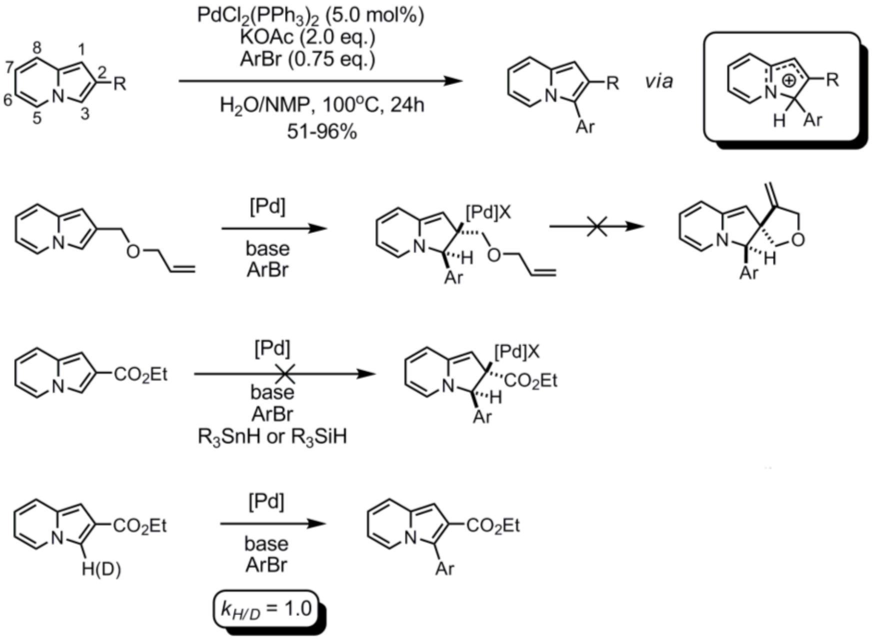


Figure 4. Proposed mechanisms for C-H bond functionalization in Pd(0)-catalyzed direct arylation.

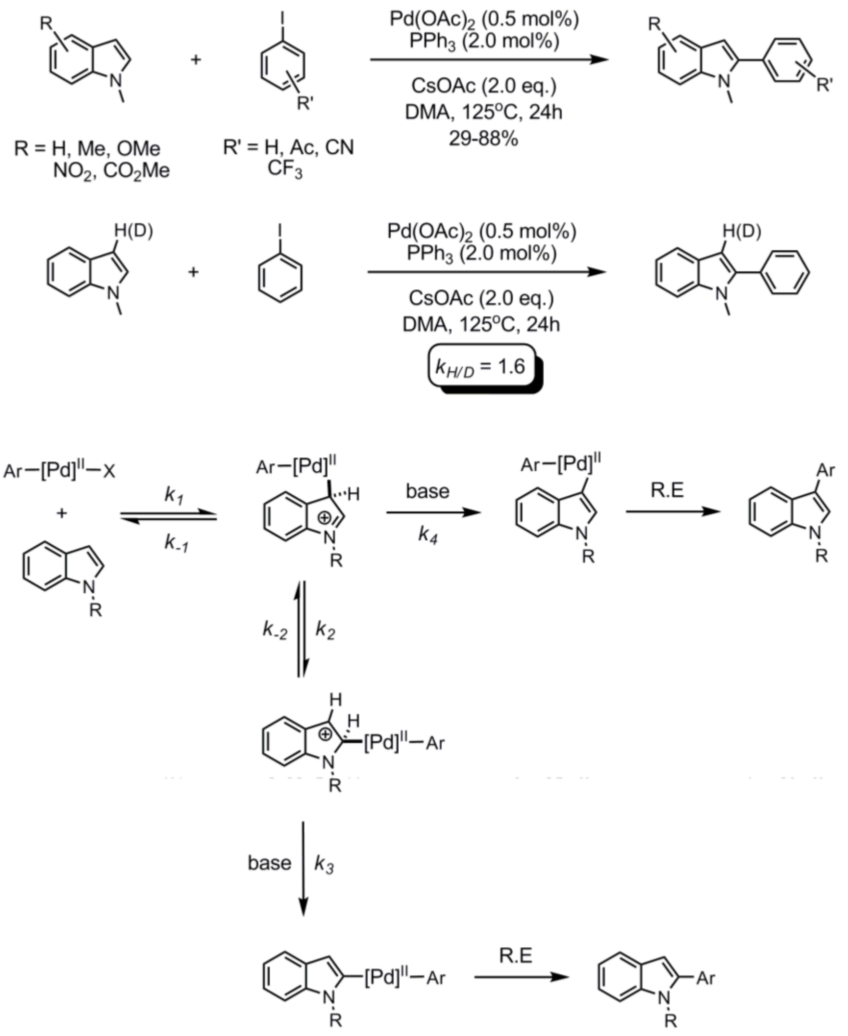
which served to eliminate the less probable pathways, thus lending support to the original S_EAr hypothesis (Scheme 20). To test the feasibility of a Heck-type carbopalladation mechanism (Figure 4d) a 2-substituted substrate was subjected to a cascade Heck reaction with the goal of forming a spiro-junction just before the final elimination of Pd. The initial C3 arylated product was obtained in good yield, but the final 5-*exo*-cyclization never occured. All attempts to perform a reductive Heck reaction using several reducing conditions failed to give the desired dihydroindolizine derivative. Dismissing carbopalladation as a plausible route, the researchers evaluated those mechanisms where the rate could be determined by a C-H bond cleavage event at the site of arylation: S_E3 or σ-bond metathesis (Figure 4b, c). For that purpose they compared the reaction rates of deuterated and non-deuterated analogues of the substrate; the experiment indicated that no KIE could be observed at C3.



Scheme 20. Gevorgyan's mechanistic study of indolizine direct arylation.

Thus, in accord with earlier reports by Miura, an S_EAr mechanism was proposed for the direct arylation of the indolizine core. A DFT calculation further reinforced the authors' conclusion, showing that the pyrrole ring of indolizine has an extended HOMO, while the LUMO mostly resides on the pyridine ring.

Sames and co-workers carried out an extensive investigation into the mechanistic rationale for the trends they observed in the direct arylation of N-methyl indole under standard Pd(0) conditions (Scheme 21)[37]. While developing their methodology, the authors discovered that the vast majority of haloarenes gave exclusively C2 arylated products with the exception of sterically demanding *ortho*-substituted ones, which led to C2/C3 product mixtures (Scheme 10). Arylation of the indole core at C2 is counter-intuitive if one tries to rationalize the process through an S_EAr mechanism because indoles are known to react with electrophiles at C3. This disparity between the predicted and observed outcomes prompted Sames to perform a series of mechanistic studies. No indication of KIE was found at C2 after the reaction kinetics were measured under pseudo-first order conditions and the findings confirmed through a competition study. However, surprisingly, the same was not true for C3, where a secondary KIE of 1.6 was measured. The involvement of direct metalation (i.e. σ-bond metathesis) was dismissed since no KIE was observed at C2. Heck-type processes were deemed equally unlikely, considering that the crucial *β*-hydride elimination step would have been problematic. The lack of rotational freedom in a carbopalladated arene would require either a very improbable *anti-β*-hydride elimination or an isomerization of the intermediate to a configuration that would allow *syn*-elimination. The latter option would involve a reversible *α*-hydride elimination proceeding *via* a



Scheme 21. Sames' S_EAr mechanism for indole arylation involving Pd C3-C2 migration.

palladium hydride-carbene intermediate, a pathway accessible to other platinum group metals (Pt, Ru), but unknown in Pd chemistry[38]. Moreover, this process is usually accompanied by a large KIE (>4.0). A Hammett plot with a negative slope (ρ = -0.71) indicating the development of a positive charge near the reaction site supported the authors' hypothesis of an S_EAr mechanism. Sames argued that the presence of a KIE does not necessarily contradict an electrophilic pathway. If the palladation step is fast and reversible ($k_{-1} > k_4$), a steady-state assumption can be made, in which case the deprotonation step (k_4) becomes kinetically relevant resulting in the observed KIE. If the deprotonation is sufficiently slow, a migration of the metal (k_2) from C3 to C2 can occur driven by the stabilizing effect of the indolic nitrogen. Thus, according to Sames, the apparent arylation at the "non-electrophilic" C2 is the result of an S_EAr process complicated by the propensity of Pd towards migration. Bulky haloarenes, however, slow down the migration process effectively propelling the reaction pathway towards C3 arylation.

Very few examples of Heck-type mechanisms are to be found in direct arylation literature. These mechanisms are generally disfavoured due to the complications with the final step - *β*-hydride elimination. As it was mentioned earlier, a highly unlikely *anti*-elimination event would be required in most cases of biaryl synthesis. A notable exception to this rule was the work on direct arylation of thiophenes and furans esterified at C3 carried out by Sharp and co-workers. Their study is summarized in section 1.2 and in Scheme 7 (page 6). As a part of the rationale for the change in regioselectivity under two different sets of conditions Sharp proposed two mechanisms, one of which was a Heck-type carbopalladation. Conceivably, the very structure of the substrate could add validity to his explanation. The presence of the carbonyl group α to the metal could allow epimerization of the palladated thiophene *via* a Pd enolate intermediate (Figure 5), leading to a facile *syn*-hydride elimination[38]. Ohta's C2 and C3 arylation of N-

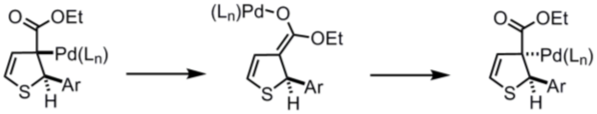
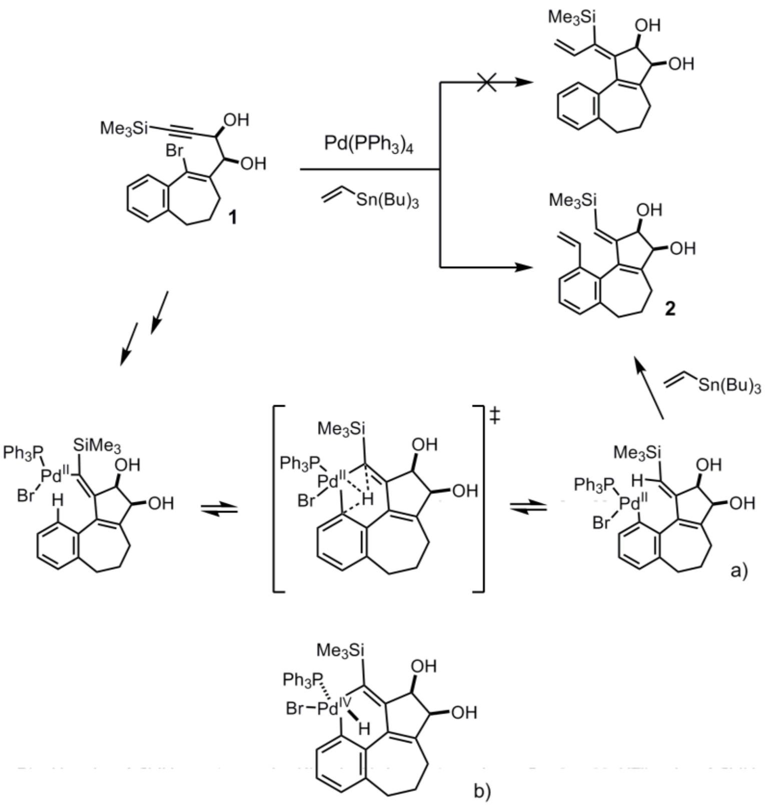


Figure 5. Epimerization of carbopalladated thiophene in Sharp's Heck-type mechanism.

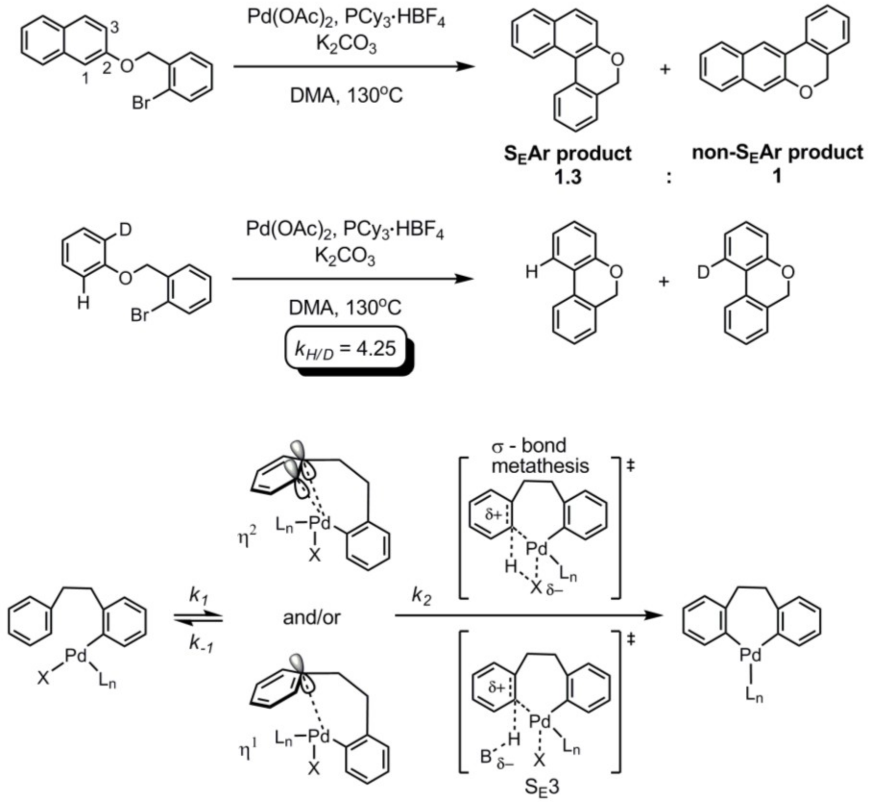
substituted indoles was also, supposedly, Heck-type in nature (Scheme 1) and considering the extremely high reaction temperature (170°C) the possibilty of a successful formal *anti β*-hydride elimination cannot be ruled out.

In recent years mechanisms involving a concerted metalation / C-H bond cleavage event (σ-bond metathesis) have been gaining more support from the experts. A pioneering theoretical study by Dedieu *et al*. on the unusual 1,5-Pd vinyl to aryl shift in *γ*-bromopropargylic-1,2 diols was the first to show the validity of the σ-bond metathesis pathway (Scheme 22a)[39]. While developing a new tandem Heck-Stille coupling reaction, the investigators were surprised to discover that upon completing the first transformation (an intramolecular Heck cyclization of the alkyne and aryl bromide), the intermediate carbopalladated species did not undergo the planned transmetallation with tributylallyl stannane. Instead, the allyl fragment was introduced onto the aryl ring. A series of DFT calculations was performed in order to pinpoint the most likely TS for the apparent migration of the metal. The process, termed "direct hydrogen transfer", was found to be concerted, involving both the vinyl and the aryl carbon centres as well as the Pd. This minimal enegry TS was favoured over the other alternative - a two-step sequence involving a C-H oxidative insertion (Figure 4e), followed by a C-H reductive elimination (Scheme 22b).



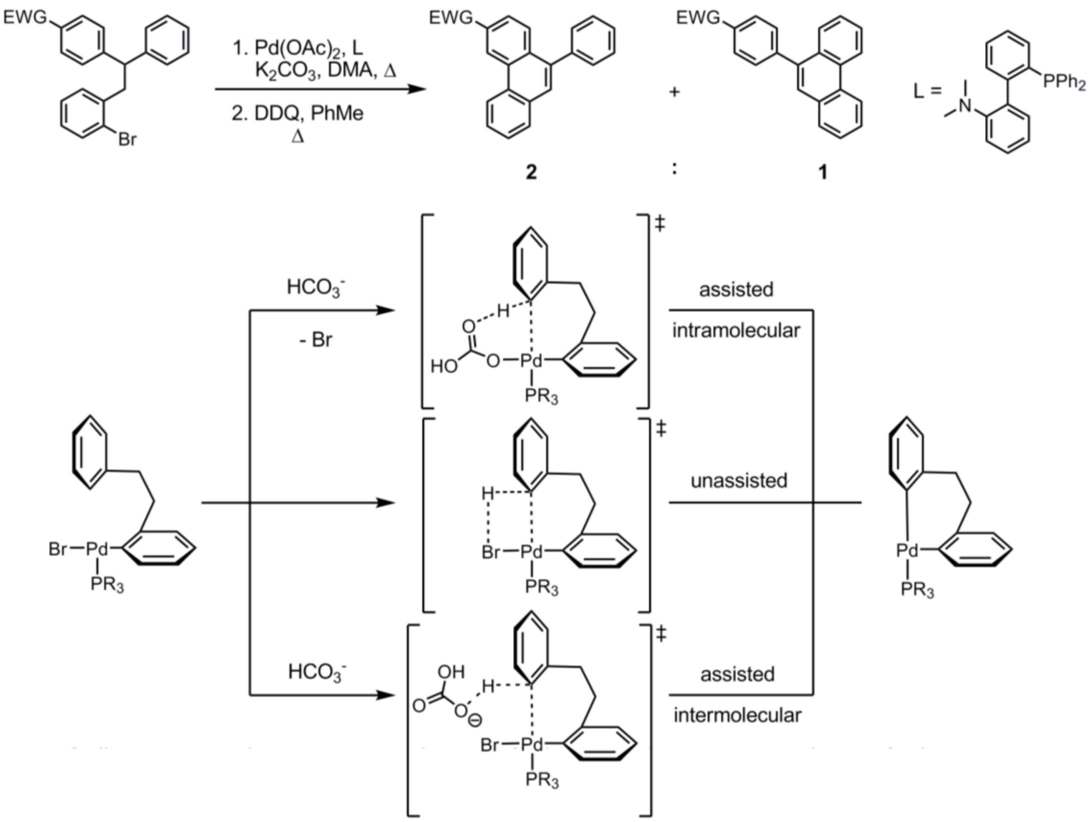
Scheme 22. Direct hydrogen transfer in 1,5 vinyl-to-aryl Pd migration (a).
Pd(IV) intermediate following C-H oxidative addition (b).

The Pd(II/IV) redox system, however, was found to be too energetically demanding (ΔG = 35.2 kcal/mol), and thus, the concerted Pd/H interchange pathway where Pd remained in +2 formal oxidation state emerged as the most probable route towards the shift of the metal centre (ΔG = 20.2 kcal/mol). The findings of Dedieu's group sparked a new interest in concerted mechanisms and shortly thereafter Fagnou and co-workers published their observations on the direct intramolecular arylation of naphthalene (Scheme 23)[40]. This substrate class undergoes electrophilic reactions at C1, however, under standard Pd(0) direct arylation conditions a significant amount of a C3 arylated product, clearly resulting from a non- S_EAr reaction, was also obtained. Kinetic experiments on a model substrate revealed a large KIE (4.25) at the site of arylation, implicating C-H bond cleavge as the rate limiting step. Following this discovery two possible mechanisms



Scheme 23. Fagnou's proposed concerted mechanism in intramolecular direct arylation.

were proposed. After the initial insertion into the aryl halide, the catalyst reversibly binds to the other coupling partner in a η^1 or η^2 fashion through the arene's π-system. The next step is the rate-determining deprotonation which could be carried out by an exogenous base (S_E3) or by one of the ligands bound to Pd (σ-bond metathesis). A similar investigation was carried out by the group of Echavarren on tethered tri-aryl substrates (Scheme 24)[41]. The researchers observed that if one of the arenes susceptible to direct arylation by the bromoarene bore an EWG, the arylation would preferentially take place at the more electron-deficient arene; these results contradicted the widely accepted S_EAr pathway. A significant KIE (6.7) was found at the site of arylation, necessitating further mechanistic investigation. DFT calculations were performed in order to establish the role of base in the reaction. Dianionic carbonate used in the reactions was approximated by hydrogencarbonate in the calculations, supposedly due to certain computational artefacts associated with the use of carbonate. Three plausible routes of deprotonation were established; the unassisted pathway, where the halide ligand acted as the base, was dismissed due to its unreasonably high free energy barrier (37.6 kcal/mol). Between the remaining two base-assisted mechanisms the intermolecular one (S_E3) was thought to be operative based on the lowest energy of activation (17.4 vs. 23.5 kcal/mol for intramolecular). At the same time the authors refrained from making decisive conclusions because in several systems due to the electronic influence of the arene substituents the intramolecular base-assisted pathway (σ-bond metathesis) was calculated to be the most accessible (13.2 vs. 14.4 kcal/mol for intermolecular).



Scheme 24. Echavarren's computational results for the role of base in intramolecular direct arylation.

These results serve to underline the vast mechanistic complexity of direct arylation reactions. Fagnou and co-workers discovered that the use of sub-stoichiometric amounts of pivalic acid (^{t}BuCOOH or PivOH) as an additive in many direct arylation protocols improves yields and allows for milder reaction conditions[42]. The researchers speculated that since the organic acid is more soluble in the reaction media than carbonate, it might be able to enter the inner coordination sphere of Pd to become more intimately involved in the C-H bond cleavage process. A generic catalytic cycle involving a pivalate ligand was proposed centering around the σ-bond metathesis step to which the term "concerted metalation-deprotonation" (CMD)

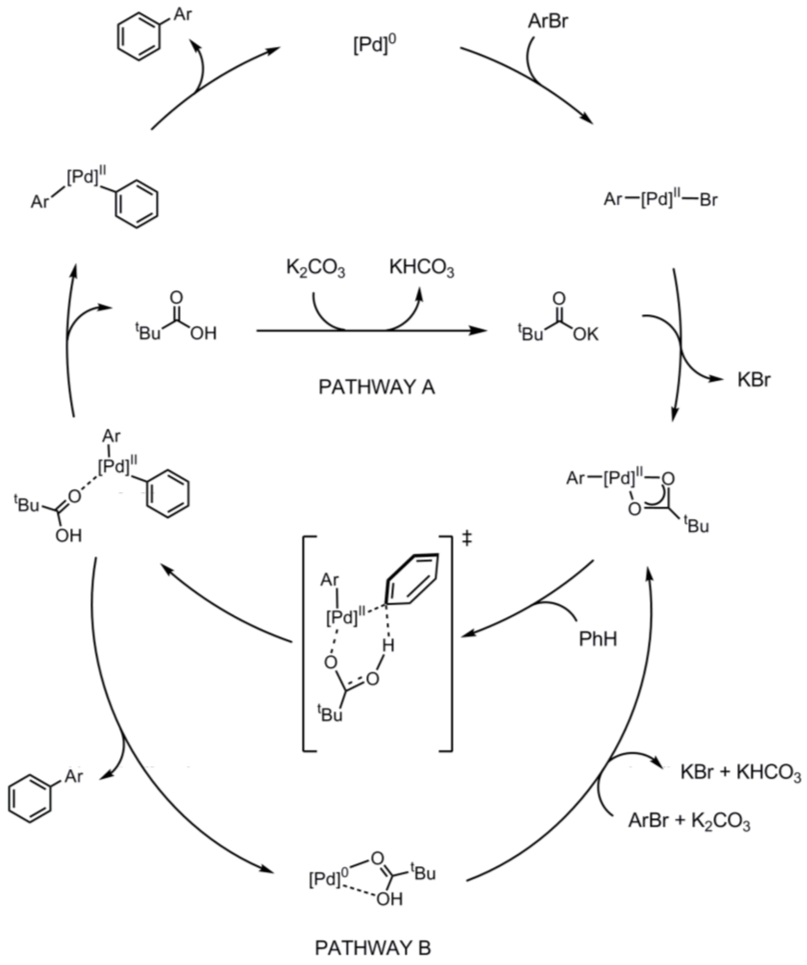
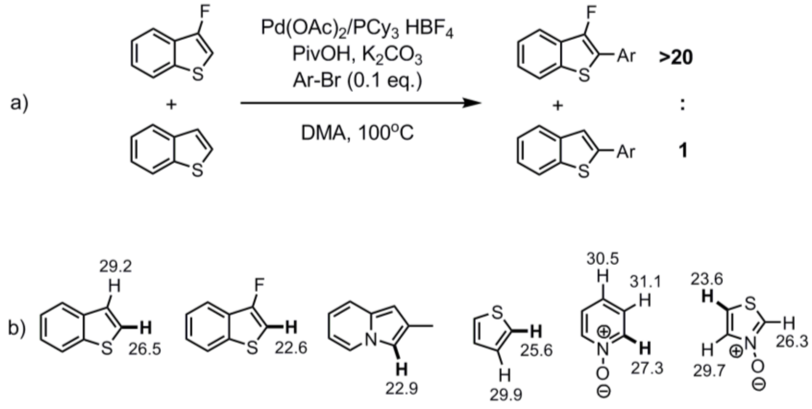


Figure 6. Fagnou's generic direct arylation catalytic
cycle based on the CMD mechanism with PivOH additive.

was applied (Figure 6). Following pivalate-assisted deprotonation two equally productive pathways were thought to be plausible: dissociation of pivalic acid from Pd and subsequent reductive elimination of the metal (pathway A) or reductive elimination of the metal and its stabilization by the coordinated pivalic acid (pathway B). The pivalic acid additive could be used in sub-stoichiometric quantities (as little as 20 mol%) in conjunction with an excess of carbonate, whose role would be to deprotonate pivalic acid making it a better ligand. The Fagnou group was particularly interested in the potential involvement of the CMD mechanism in the direct arylation of electron-deficient (hetero)arenes. These substrates have been shown to undergo efficient direct arylation, even in extreme cases such as the use of pentafluorobenzene as the substrate, seemingly violating the rules of S_EAr reactivity[52]. A competition experiment was performed where an equimolar mixture of benzothiophene and 3-fluorobenzothiophene was reacted with a small amount of an aryl halide under established conditions (Scheme 25a)[43]. Product distribution revealed that the more electron-deficient substrate was more reactive. In an attempt to explain this observation through the CMD mechanism, DFT calculations, which simulated the concerted TS were carried out on numerous (hetero)arenes. Importantly, the computationally determined arylation sites based on minimal ΔG values for the C-H bond cleavage events were perfectly correlated with the experimantally observed arylation outcomes. Moreover, these CMD-based predictions held true not only for the electron-deficient, but also electron-rich (hetero)arenes (Scheme 25b).



Scheme 25. Electron-rich vs. electron-poor arene competition study (a). Predicted ΔG values for cleavage of various C-H bonds (numbers in kcal/mol), experimantally observed arylation sites highlighted in bold (b).

Encouraged by the observation that the electron-withdrawing fluoro-group clearly had an activating effect on direct arylation substrates, the Fagnou group hypothesized that a chlorosubstituent can also be used as both an activating and a blocking group to improve reactivity at certain sites or divert them from others (Figure 7).

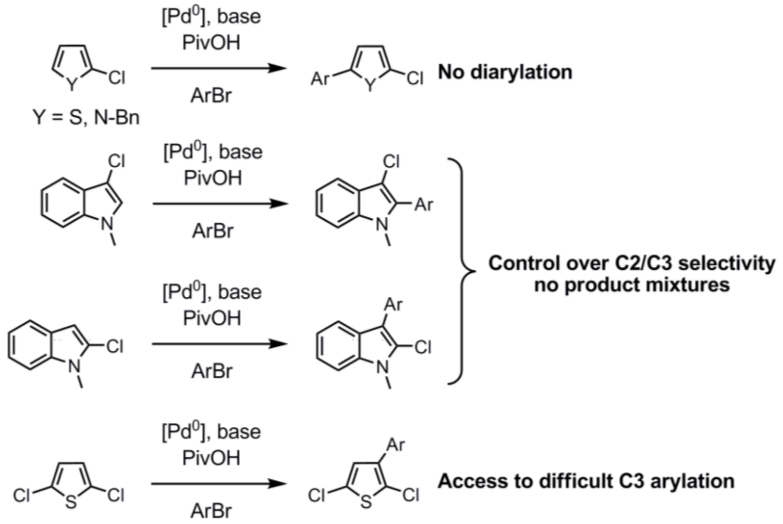


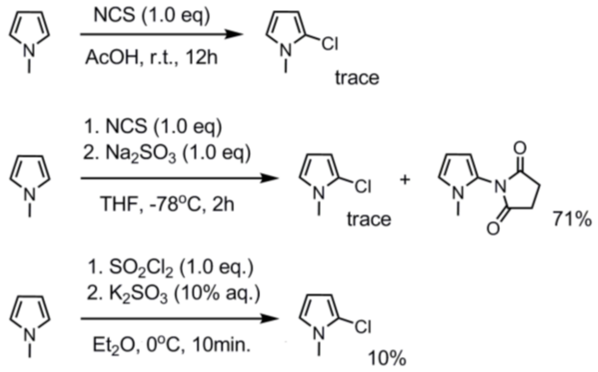
Figure 7. Impact on direct arylation regioselectivity through substrate chlorination.

Additionally, the C-Cl bond has several advantages over the flouro-group. It can be easily installed, removed, and if necessary, further functionalized through a cross-coupling process; due to the low tendency of Pd to insert into C-Cl bonds (relative to other C-X bonds) the group remains intact under most direct arylation protocols[44].

2. RESULTS AND DISCUSSION

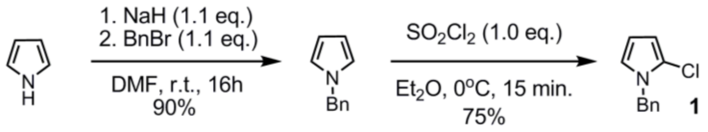
2.1 Substrate chlorination

The first substrate to undergo chlorination was commercially available freshly distilled N-methylpyrrole . Simple procedures involving electrophilic chlorinating agents consistently gave poor results (Scheme 26). Treatment with N-chlorosuccinimide (NCS) in acetic acid or DMF[45] resulted in the formation of a viscous insoluble polymer with only a trace of the desired



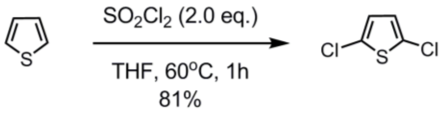
Scheme 26. Efforts in chlorination of N-methylpyrrole.

product. An alternative procedure involving an addition of sodium sulfite[46] gave a pyrrole-succinimide adduct as the major product. Treatment with sulfuryl chloride at low temperatures[47] was also found to be ineffective and was accompanied by the formation of the polymer. Unprotected pyrrole as well as N-methylpyrrole are very reactive compounds, known to undergo facile polymerization, especially under acidic conditions[46]. The chlorinated species are markedly unstable and difficult to store. Furthermore, the volatility of the product complicated its purification and use. In the course of distillation, due to the presence of numerous by-products, among which were (poly)chlorinated regioisomers, obtaining a clean fraction of the product was impossible. A simple change of the nitrogen protecting group resulted in a much easier chlorination process. Commercially available pyrrole was benzylated and subsequently treated with sulfuryl chloride in dry ether at 0°C. The reaction was fast and afforded the product (**1**) in 75% yield (Scheme 27). The increased steric bulk of the molecule possibly helped to slow down the polymerization process and the decrease in volatility allowed purification by column chromatography. The much poorer electron-donating ability of the benzyl group compared to the methyl group may have also attenuated the nucleophilicity of pyrrole, leading to fewer by-products as a result.



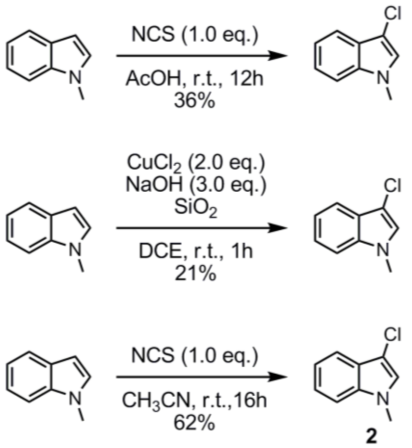
Scheme 27. Electrophilic chlorination of N-benzylpyrrole.

For thiophene-related experiments commercially available 2-chlorothiophene and 2,5-dichlorothiophene were used; however, to illustrate the simplicity of thiophene chlorination, thiophene was treated with 2 equivalents of sulfuryl chloride and heated in dry THF[48]; the product, whose spectral characteristics were identical to those of the commercial substrate, was obtained in 81% yield (Scheme 28).



Scheme 28. Dichlorination of thiophene.

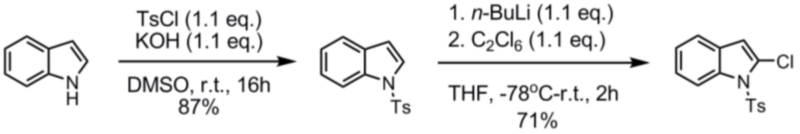
Simple chlorination routes to obtain 3-chloro-N-methylindole (**2**) were tested on commercial N-methylindole; initial attempts using electrophilic agents proved to be low-yielding (Scheme 29). NCS in acetic acid[49] only gave 36% of the product. The use of copper (II) chloride under



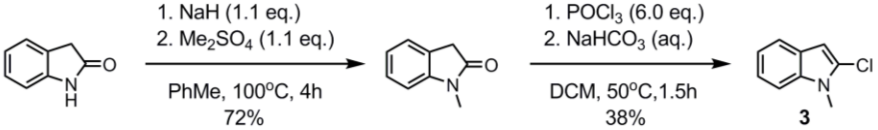
Scheme 29. Preparation of 3-chloro-N-methylindole.

basic conditions[50] resulted in a small amount of the product and led to the formation of numerous by-products. After several experiments the optimal system was found to be NCS in acetonitrile; the product was obtained in 62% yield. The absence of strongly alkaline or acidic conditions likely minimized the formation of indole dimers, polymers, and over-halogenated by-products.

Due to the fact that indole reacts with electrophiles at C3, no simple one-step procedure for the preparation of 2-chloro-indole derivatives was available. Typically, their synthesis involves lithiation of the substrate at C2, followed by treatment with a chlorinating agent[51]. The electron rich N-methylindole is poorly suited for chlorination *via* deprotonation with the less reactive and easy to handle organolithium reagents, such as *n*-BuLi. To overcome this limitation a directing group is usually introduced onto the nitrogen to facilitate lithiation at C2. Alternatively, a strongly electron-withdrawing nitrogen protecting group may be used to increase the acidity of the C2 proton. In order to capitalize on both strategies, N-tosylindole was prepared and then subjected to treatment with *n*-BuLi, followed by hexachloroethane; the desired product was obtained in 71% yield (Scheme 30). Unfortunately, the new substrate was absolutely inert under direct arylation conditions. Given the observation by the Fagnou group that electron-deficient (hetero)arenes readily undergo direct arylation under typical Pd(0)-catalyzed conditions[52], the strongly electron-withdrawing nature of the tosyl group may not have been at the root of this puzzling lack of reactivity. A possible explanation could stem from the coordinating ability of the Lewis basic oxygens present on the tosyl moiety. Thus, the Pd catalyst could have been directed to arylate the unavailable C2 position, leading to a disruption in the catalytic cycle. This type of coordination-assisted arylation of indoles was described by Djakovich and summarized in Scheme 15 (page 12)[26]. In a similar fashion, Sanford used the nitrogen of 2-phenylpyridine as a directing group to carry out Pd-catalyzed *ortho*-halogenation of the phenyl moiety[49]. In light of the failure of 2-chloro-N-tosylindole as a viable substrate, a new strategy was developed based on the reaction of oxindole with phosphorous oxychloride in a Vilsmeier-Haack fashion (Sceme 31)[53]. The desired product is obtained by transforming the oxindole substrate into a chloroiminuim intermediate, at which point the reaction is quenched. First, N-methyloxindole was prepared from commercially available oxindole and subsequently, a variety of reaction conditions was examined to obtain a useful yield of the chlorinated product (**3**).



Scheme 30. Preparation of 2-chloro-N-tosylindole.



Scheme 31. Preparation of 2-chloro-N-methylindole from oxindole.

The optimization study was monitored qualitatively by TLC, taking into account product formation and, more importantly, decomposition. Eventually, through careful adjustment of parameters like reaction time and temperature, equivalents of the chlorinating agent, and the use of additives, decomposition and formation of by-products were minimized; however, the product was only obtained in 38% yield (91% based on recovered starting material) (Table 1). The inability to obtain a higher yield of the product can be explained by the tendency of the crude product to degrade. Indeed, the reaction mixture required immediate work-up and purification to avoid any loss of the product. During his study of chloroindoles, Powers determined that one of the main decomposition pathways of the chloroiminium salt was hydrolysis upon quenching with aqueous sodium bicarbonate[53]. The presence of small amounts of HCl in the reaction medium could have been also detrimental, since protonation at C3 would have left the C2 position particularly vulnerable to a nucleophilic attack , resulting in hydrolysis and/or formation of dimers[53]. Unfortunately, the addtion of a base (Et_3N) to the reaction mixture did not improve the yield, but induced the formation of an insoluble by-product.

Table 1. Optimization efforts in the chlorination of N-methyloxindole.

Time (h)	Temp (^oC)	$POCl_3$ eq.	additive
0.5	0	1.0	[✓ DCM]
1.0	r.t	3.0	DCE
[✓ 1.5]	30	[✓ 6.0]	TsOH
2.0	40	neat	Et_3N
2.5	[✓ 50]		PCl_5
3.0	60		

2.2 C5 direct arylation of chlorinated pyrrole and thiophene

The chlorinated pyrrole **1** was subjected to direct arylation with various aryl bromides under conditions developed by the Fagnou group for a wide range of heteroarenes (Figure 8)[54]. The arylated products **10-14** were obtained as single regioisomers (isolated yields given) with no traces of di-arylation. The yields varied depending on the electronic nature of aryl bromides. Electron-rich bromoarenes consistently gave lower yields than electron-neutral and electron-deficient ones. The yields were improved by using aryl iodides instead of bromides, as in the case of **10**. In all likelihood, electron-poor aryl bromides possess a weakened carbon-halogen bond, making oxidative insertion of the catalyst a very fast step. On the other hand, electron-donating substituents strengthen the carbon-halogen bond of the haloarene through inductive and

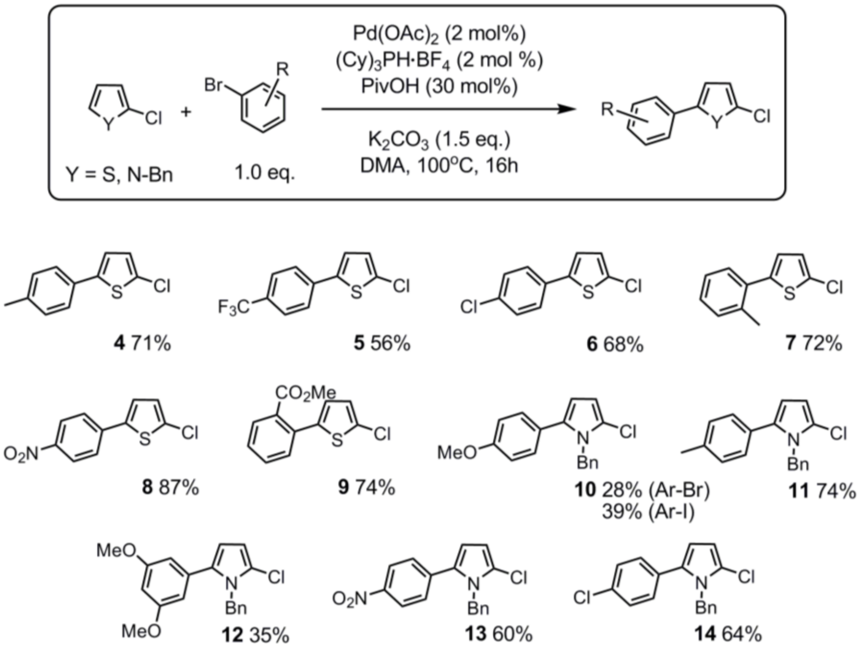


Figure 8. Reaction scope for direct arylation of chlorinated pyrrole and thiophene.

resonance-based effects. As a result, oxidative insertion into the carbon-chlorine bond of the heteroarene becomes competitive and kinetically relevant with respect to the catalyst's insertion into the carbon-bromine bond[44]. The introduction of aryl iodides, which possess the weakest of all carbon-halogen bonds steers the reaction towards the desired product.

Similarly to the pyrrole substrate, 2-chlorothiophene was subjected to the conditions outlined in Figure 8. No signs of di-arylation were found during the isolation of products **4-9** (isolated yields given). The steric nature of aryl halides was found to have no influence on reaction outcomes; however, as in the case of pyrrole, the best results were observed with electron-neutral and electron-deficient aryl bromides. The enhancement of regioselectivity attained through the use of a chloride blocking group at C2 presents a synthetic strategy complimentary to the methods described in Section 1.2. The vast majority of these protocols rely on blocking one of the reactive sites on the heteroarene to avoid di-arylation. In rare cases (such as Sharp's arylation of thiophene) a C3-substituted substrate was employed, however, the selectivity and yield of direct arylation suffered under such conditions. Moreover, C3 functionalization of pyrrole and thiophene *via* conventional methods is a laborious venture, reflected in the cost of these substrates[55]. Chlorinated heteroarenes are compatible with bromo- or iodoarenes as coupling partners; a large variety of inexpensive bromoarenes are available commercially. The versatility of the chloride group is exemplified by the wide availability of inexpensive chlorinating agents and the simplicity of chlorination procedures[44]. Occasionally, as in the case of 2-chloro-N-methylindole, the preparation of the desired chlorinated derivative may be somewhat problematic, but the overwhelming majority of heteroaromatics investigated by the Fagnou group in relation to the present project underwent chlorination with no challenges[44]. Unlike many of the 2-substituted pyrroles and thiophenes described in the literature (those bearing an alkyl, cyano, or ester group), chlorinated heterocycles can be subjected to reductive de-chlorination following direct arylation in order to reveal the C2 site. Several examples of this transformation applied to a number heteroarenes were disclosed by the Fagnou group[44] and some of the products are described in this text (Section 2.4). Alternatively, the carbon-chlorine bond of the arylated product can be potentially functionalized *via* a Suzuki cross-coupling following Buchwald's conditions[56] or a Heck reaction under the conditions developed by Fu[57]. The feasibility of both transformations was demonstrated by the Fagnou group[44].

2.3 C2 or C3 direct arylation of chlorinated indole

Both chlorinated indole substrates **2** and **3** reacted smoothly with a range of aryl bromides under the conditions described previously to give products **15-23** (isolated yields) (Figure 9). The same electronic bias in favour of electron-poor aryl bromides was observed as in the case of pyrrole and thiophene. The use of an aryl iodide in the preparation of compound **19** increased the yield four-fold. Through selective blocking of the indoles' reactive sites, complete control over C2/C3 regioselectivity of arylation was established. Strategies for regioselective direct arylation of indole that are found in the literature rely either on blocking (or hindering) one of the reactive sites or manipulation of the reaction conditions. The chlorination methodology presented in this text resembles the former approach, favoured by Sames, Djakovitch, and others (Section 1.3), however, as in the case of pyrrole and thiophene, the potential of the carbon-chlorine bond to undergo various transformations may prove to be advantageous. Moreover, in the course of several competition experiments it was shown that chlorinated heteroaromatics undergo direct arylation faster than their unhalogenated analogues. The activating role of the chloride group is examined and discussed in detail in Sections 2.5 and 2.6. A number of direct arylation protocols forego the use of blocking groups and, instead, rely on unconventional

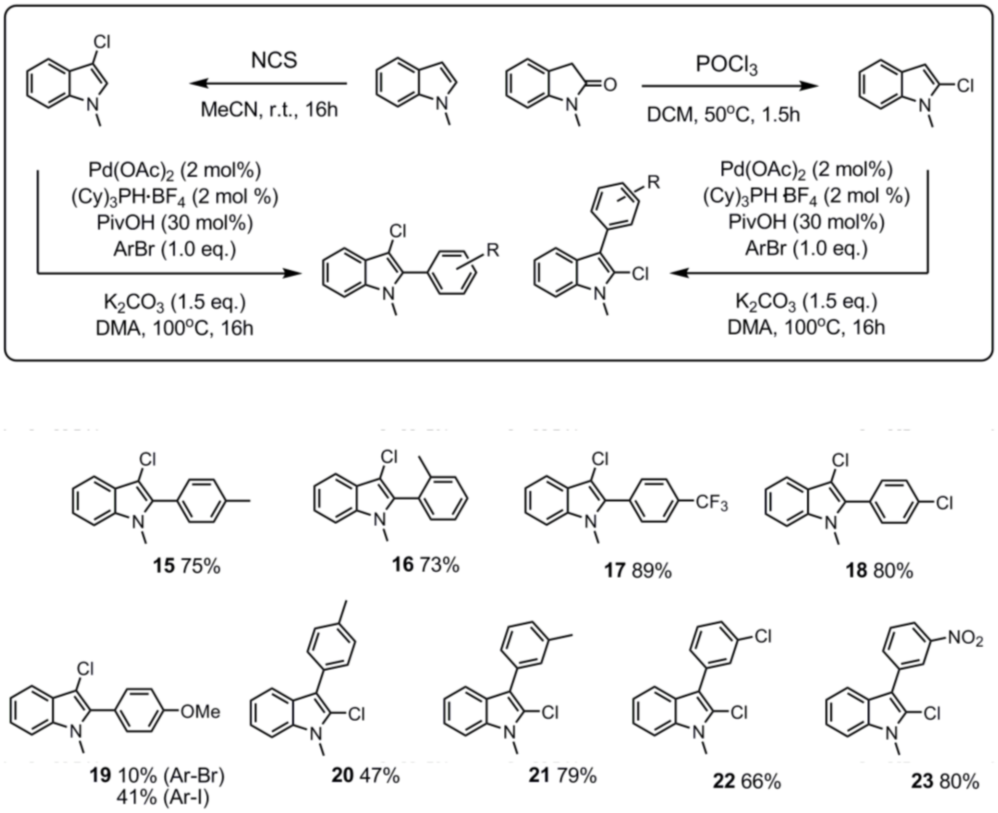
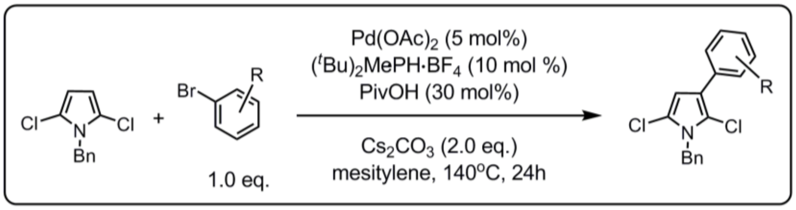


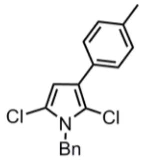
Figure 9. Reaction scope for direct arylation of chlorinated indole.

catalysts and additives to achieve the desired outcome. In most cases the effectiveness of these approaches is comparable to the chlorination methodology in terms of benefits and drawbacks. For example, the protocols developed by Zhang and Bellina (Section 1.3) are both highly C3 selective, typically high-yielding, and can be carried out in one step. On the negative side, both are intolerant to electron-poor aryl bromides, Zhang's procedure requires the expensive POPd catalyst[58], and Bellina's method does not tolerate N-protected indoles. In comparison, the use of chlorinated indoles offers complete regioselectivity and good yields, but requires N-protection and electron-poor or neutral aryl halides for best results.

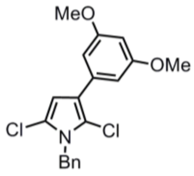
2.4 C3 direct arylation and derivatization of chlorinated thiophene

In the process of pyrrole chlorination a small amount of 2,5-dichloro-N-benzylpyrrole was formed as a by-product. It was thought that C3 arylated derivatives could be obtained from it, since the most reactive positions were blocked. In a related study, a new set of conditions was developed by the Fagnou group specifically designed to force direct arylation towards less reactive sites on heteroarenes[44]. Since its discovery, the methodology had been successfully applied to several azoles, but was never tested on pyrrole. The application of these forcing conditions to 2,5-dichloro-N-benzylpyrrole, unfortunately, gave discouraging results. Even at 140°C the reaction was sluggish, with low conversions and isolated yields of the desired products (Figure 10).





24 15%

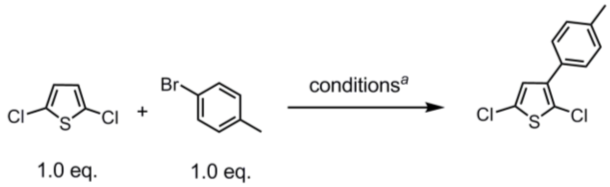


25 12%

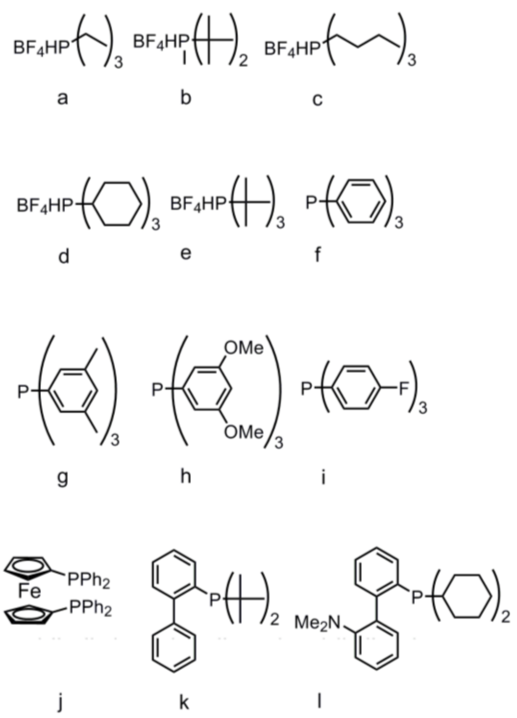
Figure 10. Attempted C3-arylation of 2,5-dichloro-N-benzylpyrrole.

Despite the initial set-backs a decision was made to pursue the challenge with a new target in mind. Considering the wide applicability of 3-arylthiophene derivatives in the field of organic electronics, a full re-optimization of the conditions presented in Figure 41 with 2,5-dichlorothiophene as the substrate was undertaken. The investigation began with a ligand screen (Table 2). Electronic and steric effects of the ligands were examined, a bi-dentate lgand

Table 2. Ligand screen for the direct C3 arylation of 2,5-dichlorothiophene.



Entry	Ligand	GC yield (%)^b	C3,C4 di-arylation (%)
1	a	21	-
2	b	61	-
3	c	38	-
4	d	51	-
5	e	33	-
6	f	46	-
7	g	41	-
8	h	35	-
9	i	45	-
10	j	23	-
11	k	20	-
12	l	17	-

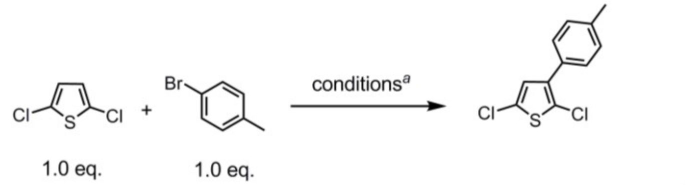


[a] Conditions: $Pd(OAc)_2$ (5 mol%), ligand (10 mol %), PivOH (30 mol%), Cs_2CO_3 (2.0 eq.), mesitylene (0.3M), 140°C, 24h

[b] Conversions obtained by GC-MS analysis with 5μL of 30mg/mL solution of 1,3,5-trimethoxybenzene as an internal standard

was screened as well. The electron-rich pre-ligand of medium bulk, $(^tBu)_2MePHBF_4$ gave the best result, whereas the biphenyl-based Buchwald ligands, and the bi-dentate DPPF ligand were the least effective. The inferior performance of Buchwald ligands could have been caused by cyclopalladation of the biphenyl, a well known pitfall of the earlier generation of these ligands[59]. The low molecular weight $(Et)_3PHBF_4$ was likely volatilized during the reaction (bp = 127°C). Next, a solvent screen was carried out, where the polarity of the solvents increased gradually from mesitylene to ^{t}BuOH; aprotic and protic solvents, as well as a mixture of two solvents were tested (Table 3). Due to significant differences in boiling points, all the solvents were heated to 100°C. The lowest GC yields were obtained at the lower and upper limits of polarity; such was the case with mesitylene, ^{t}BuOH, and the aprotic DMSO. The best solvent was the moderately polar aprotic ^{i}PrOAc. As the arylation process became more favourable, small amounts of

Table 3. Solvent screen for the direct C3 arylation of 2,5-dichlorothiophene.



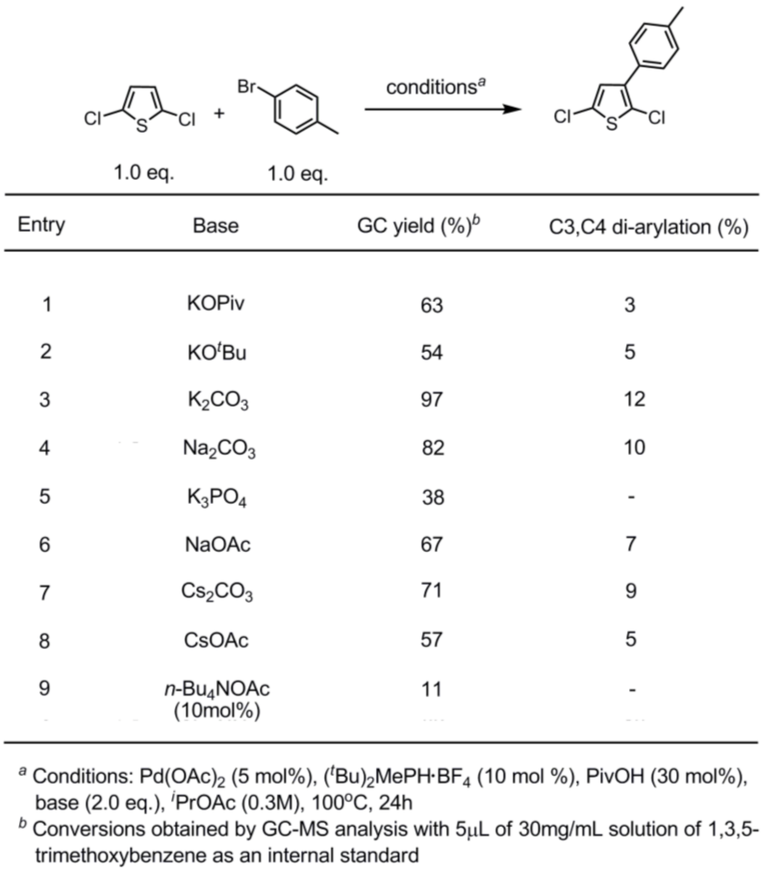
Entry	Solvent	GC yield (%)^b	C3,C4 di-arylation (%)
1	mesitylene	13	-
2	dioxane	58	2
3	^{i}PrOAc	71	6
4	DMA	23	trace
5	DMSO	18	-
6	^{t}BuOH	15	-
7	^{t}BuOH/DMA 2/1	20	-

[a] Conditions: $Pd(OAc)_2$ (5 mol%), $(^tBu)_2MePH \cdot BF_4$ (10 mol %), PivOH (30 mol%), Cs_2CO_3 (2.0 eq.), solvent (0.3M), 100°C, 24h

[b] Conversions obtained by GC-MS analysis with 5μL of 30mg/mL solution of 1,3,5-trimethoxybenzene as an internal standard

a C3,C4-diarylated by-product were detected in the crude reaction mixture. A screen of bases was also performed (Table 4). Carbonates and acetates of lighter alkali metals (Na, K) were best suited for the reaction, with K_2CO_3 giving a very high 97% GC yield of which 12% was due to di-arylation. An acetate with an organic counterion ($(n\text{-Bu})_4NOAc$) was also tested, but gave poor results. Similar ammonium salts were shown to be extremely beneficial in a series of Cu-catalyzed C-N bond forming reactions, supposedly, because of their high solubility in organic media[60].

Table 4. Base screen for the direct C3 arylation of 2,5-dichlorothiophene.



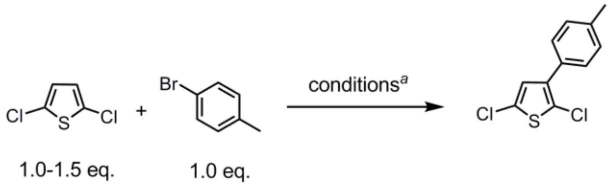
Entry	Base	GC yield (%)[b]	C3,C4 di-arylation (%)
1	KOPiv	63	3
2	KO^tBu	54	5
3	K_2CO_3	97	12
4	Na_2CO_3	82	10
5	K_3PO_4	38	-
6	NaOAc	67	7
7	Cs_2CO_3	71	9
8	CsOAc	57	5
9	$n\text{-Bu}_4NOAc$ (10mol%)	11	-

[a] Conditions: $Pd(OAc)_2$ (5 mol%), $(^tBu)_2MePH{\cdot}BF_4$ (10 mol %), PivOH (30 mol%), base (2.0 eq.), ^{i}PrOAc (0.3M), 100°C, 24h

[b] Conversions obtained by GC-MS analysis with 5μL of 30mg/mL solution of 1,3,5-trimethoxybenzene as an internal standard

Lastly, the new conditions were fine-tuned by examining parameters like the source of Pd, reaction temperature, amount of base, and catalyst loading (Table 5). $Pd(OAc)_2$ was found to

Table 5. Final optimization for the direct C3 arylation of 2,5-dichlorothiophene.

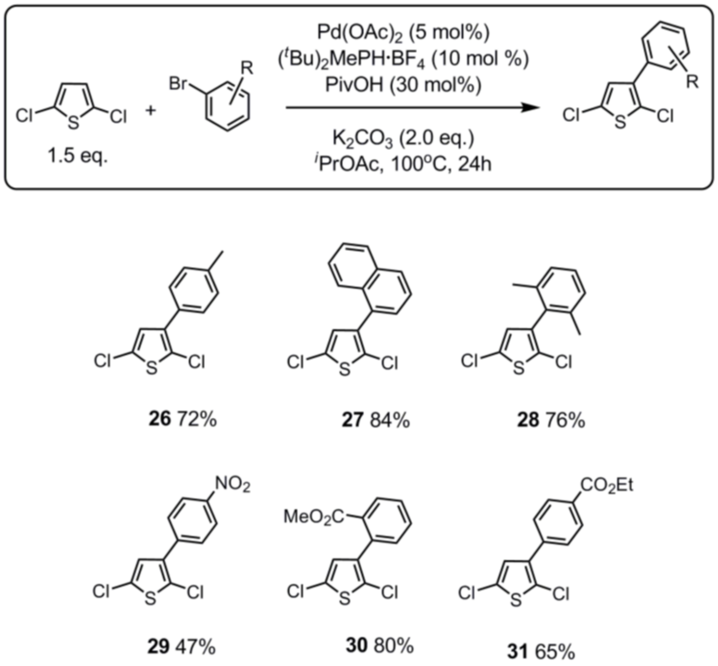


Parameter	GC yield (%)[b]	C3,C4 di-arylation (%)
Pd source		
$Pd(OAc)_2$	97	12
$Pd_2(dba)_3$	85	10
Temp (°C)		
80	67	2
90	79	7
100	97	12
Equiv. of base		
1.0	43	-
1.5	68	4
2.0	97	12
Pd loading (mol%)		
1.0	56	trace
2.0	73	6
5.0	97	12
Additive		
CuI	trace	-
Equiv. of thiophene		
1.5	98	5

[a] Conditions: $[Pd^0]$, $(^tBu)_2MePH\cdot BF_4$, PivOH (30 mol%), base, ^{i}PrOAc (0.3M), Δ, 24h

[b] Conversions obtained by GC-MS analysis with 5μL of 30mg/mL solution of 1,3,5-trimethoxybenzene as an internal standard

give slighlty better results than $Pd_2(dba)_3$, 100°C was the optimal temperature and, likely, the highest possible for reactions run in ^{i}PrOAc. Two equivalents of K_2CO_3 were necessary to achieve the highest GC yields. The optimal Pd loading was found to be 5 mol%; the effect of stoichiometric CuI additive, sometimes beneficial in direct arylation of azoles[61], was found to be detrimental. Copper salts are thought to assist arylation processes by activating the heterocycle through base-assisted cupration of the reactive C-H bond. Subsequently, a facile transmetallation with aryl-palladium or an uncatalyzed Ullmann-type coupling with an aryl halide can take place and both processes generate CuX. Possibly, cupration of the thiophene C3-H bond is slow enough to allow Cu to compete with Pd for inserting into the carbon-bromine bond of the bromoarene and interfere with the catalytic cycle. Finally, the issue of the unwanted C3,C4 di-arylation was addressed; the use of a slight excess of 2,5-dichlorothiophene (1.5 equiv.) decreased the formation of the by-product from 12% to 5%. With the new set of conditions developed, the scope of the reaction was investigatetd. Considering the prevalence of electron-withdrawing substituents in thiophene-based materials[29], several electron-neutral and electron-poor aryl bromides were tested, leading to products **26-31** (isolated yields given). The yields ranged from medium to high (Figure 11), the amount of the di-arylation by-product



26 72%

27 84%

28 76%

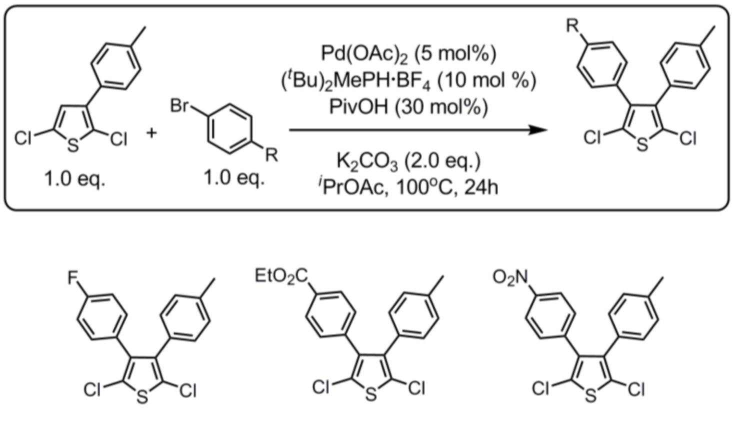
29 47%

30 80%

31 65%

Figure 11. Direct C3 arylation of 2,5-dichlorothiophene.

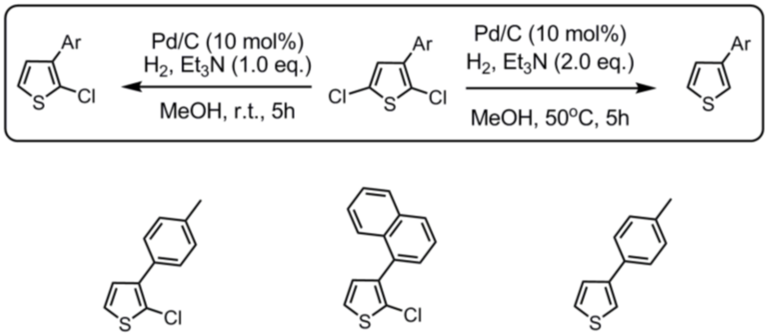
was at its minimum when sterically bulky bromoarenes were used. A natural step following C3 arylation would be to attempt derivatization through a second arylation at the available C4 position. The substrate of choice for this study was 2,5-dichloro-3-*p*-tolylthiophene **26**. The products of the second arylation **32-34** (isolated yields given) were obtained in medium yields (Figure 12). Since C4 arylation was the desired reaction outcome, there was no need to use an excess of the thiophene. The ability of 2,5-dichlorothiophene to undergo two sequential direct arylations under the newly developed conditions may prove to be a valuable way of introducing molecular complexity into polythiophene precursors. To date, most 3-arylthiophene syntheses use Suzuki and Stille couplings or Grignard reagents, and rely on expensive staring materials[29]. All starting materials required for the arylation of 2,5-dichlorothiophene are readily available and inexpensive, and the reaction conditions are mild. Overall, this methodology lends itself well to the research needs in the field of polythiophene materials, where polymer tuning often depends on rapid production of a wide range of monomers with varying substituents. The C3 arylated products were also subjected to reductive de-chlorination using Pd/C and H_2[62]. An intriguing discovery emerged from the hydrogenation studies. In the presence of one equivalent



32 49% **33** 68% **34** 31%

Figure 12. Direct C4 arylation of 2,5-dichloro-3-*p*-tolylthiophene.

of Et_3N at room temperature only one chloride group was removed regiospecifically from C5, most likely due to steric reasons. When the reaction mixture was heated to 50°C and two equivalents of Et_3N were used, the dechlorination process took place at both C2 and C5 (Figure 13). The products were typically obtained in excellent yields.



35 85% **36** 91% **37** 95%

Figure 13. Selective de-chlorination of C3 arylated thiophenes.

The presence of chloride groups on the C3 arylated products has the potential to facilitate the process of polymerization. The monomeric units are linked through the C2 and C5 positions. The more sterically hindered C2 position is known as the "head", while C5 is called the "tail". Two units can be potentially joined in three ways: "head-to-head" (HH), "head-to-tail" (HT), and "tail-to-tail" (TT) (Figure 14). The regioregularity of the polymer is extremely important for its

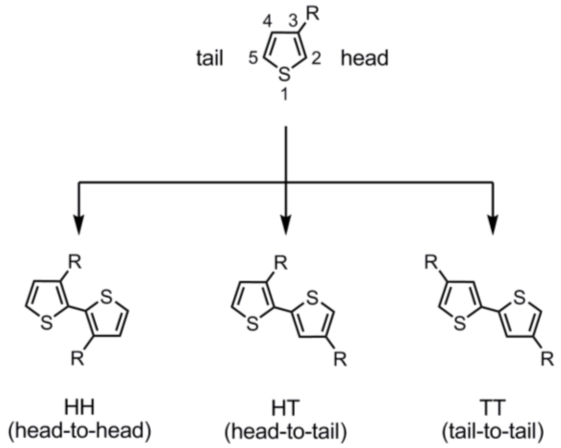
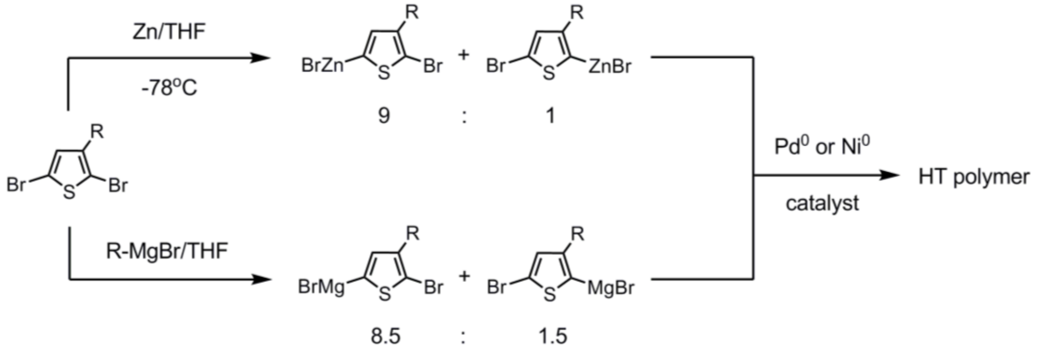


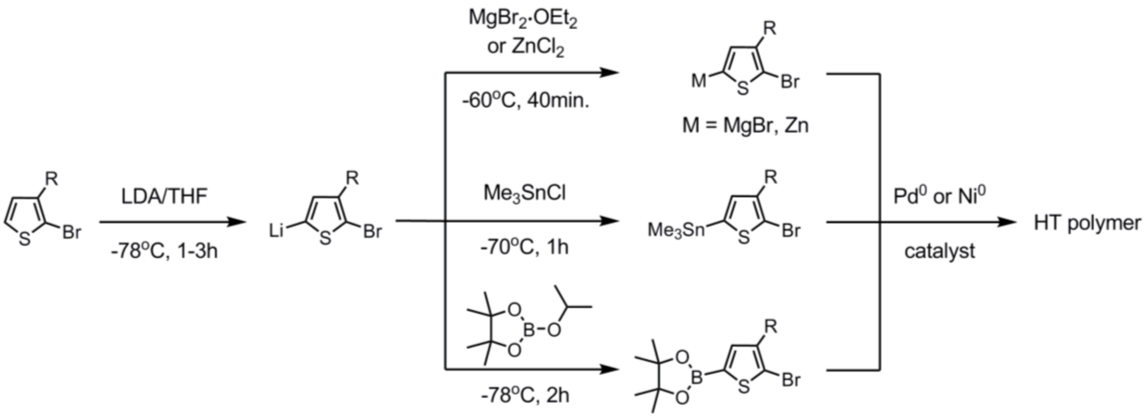
Figure 14. 3-substituted thiophene coupling patterns.

performance[29]. It is known that polythiophenes with a high HT content have the best electronic properties[29]. These polymers have the highest degree of planarity, owing to minimal steric interactions between C3 groups. Consequently, two-dimensional charge transport along the extended π-system is very efficient. De Leeuw and co-workers showed that HT poly(3-hexylthiophene) can support a current of high mobility (0.1 $cm^2\ V^{-1}\ s^{-1}$) and density (28 mC m^{-2})[63]. In order to minimize the degree of randomness in the coupling process, several synthetic strategies for controlled HT thiophene polymerization have been developed. Some of them utilize 2,5-dibromo-3-substituted thiophenes, prepared by bromination of 3-substituted thiophenes (Scheme 32). Rieke's method reacts the starting material with "Rieke zinc" to generate mostly C5 metallated intermediate; polymerization occurs in the presence of a Pd or Ni catalyst to afford the HT polymer exlusively[64]. A similar strategy, known as Grignard metathesis



Scheme 32. Polythiophene syntheses based on 2,5-dibromo-3-substituted thiophenes.

(GRIM), was developed by the group of McCullough; it conveniently uses commercially available pre-formed Grignard reagents to metalate the monomer *via* a magnesium-halogen exchange[65]. Given the well-established synthetic precedent for brominated thiophene, it is possible to imagine that 2,5-dichloro-3-substituted thiophenes may also be utilized in this fashion, especially in light of the report by Sone and co-workers, where 2,2'-bithienyls were generated from 2-chloro-4-arylthiophenes in the presence of Zn metal and a $NiCl_2/PPh_3$ catalyst[66]. Also, as mentioned previously, a number of cross-coupling protocols for aryl chlorides has been developed. The regioselectivity of reductive de-chlorination which led to the formation of products **35** and **36** also may be applied to ahieve HT regioregularity in the synthesis of polythiophenes. Several groups have used 2-bromo-3-substituted thiophenes as substrates biased towards HT coupling (Scheme 33). First, in 1993 McCullough reported a Kumada coupling

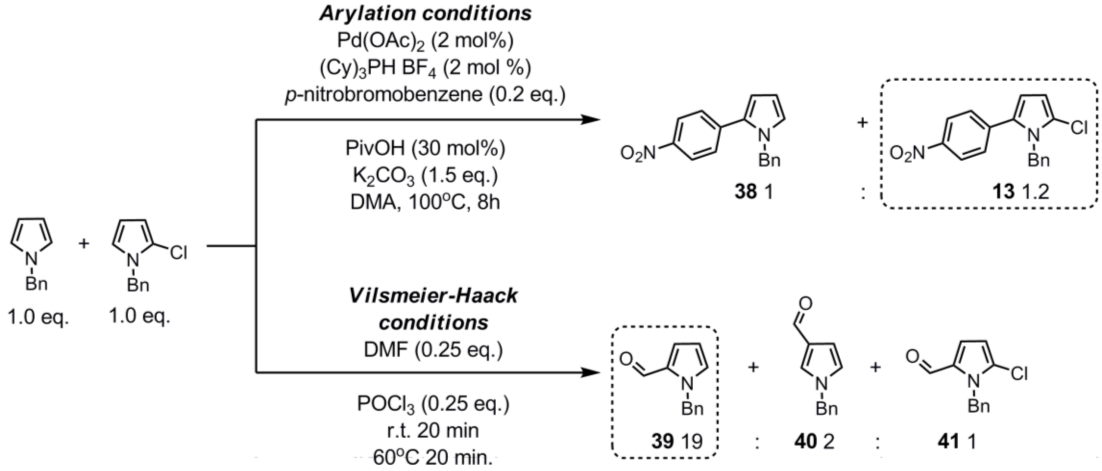


Scheme 33. Polythiophene syntheses based on 2-bromo-3-substituted thiophenes.

protocol, where the organomagnesium species was derived from a C5 lithiated thiophene[67]. Shortly thereafter, Barker disclosed a Stille coupling method[68], followed by Bidan with his Suzuki cross-coupling strategy[69].

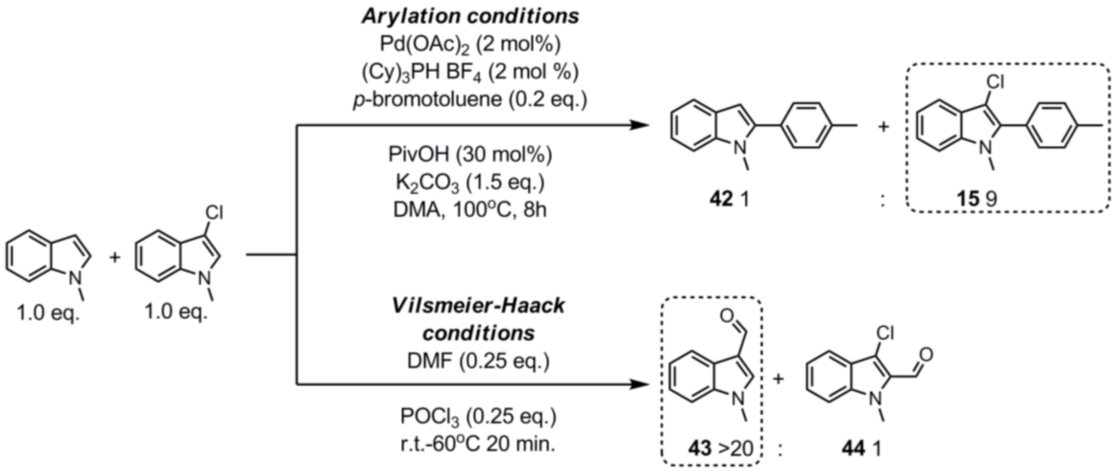
2.5 Mechanistic studies: competition experiments

In order to find out if the chloride group has an activating effect on the heteroaromatic substrates, several competition experiments were conducted. The results were obtained by analyzing the ^{1}H NMR spectra of the crude reaction mixtures. In the first instance, an equimolar mixture of N-benzylpyrrole and 2-chloro-N-benzylpyrrole was submitted to direct arylation conditions with a small amount (0.2 equivalents) of *p*-nitrobromobenzene (Scheme 34). The aryl bromide was used as a limiting reagent to determine which of the two substrates reacts with it preferentially at the early stages of the reaction. Each of the reaction products was synthesized and fully characterized beforehand in order to make the interpretation of the competition NMR spectrum possible. The analysis revealed that the chlorinated substrate reacted with the bromoarene slightly faster, leading to a 1.2 : 1 product distribution in favour of **13**. In a similar experiment the same pair of pyrroles was subjected to Vilsmeier-Haack



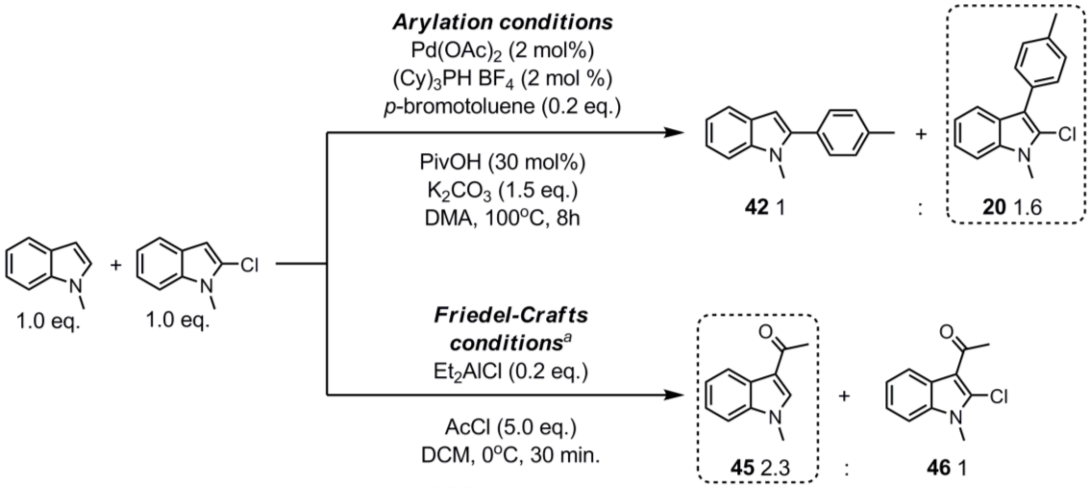
Scheme 34. Direct arylation and S_EAr competition studies for pyrrole.

formylation, a reaction known to follow the S_EAr pathway, with only 0.25 equivalents of the Vilsmeier reagent. The distribution of products was very different from the previous case: the non-chlorinated substrate reacted much faster, resulting in a >20 : 1 product ratio. As in the previous case, the aldehydes **39**, **40**, **41** were synthesized and characterized prior to the experiment. The next substrate to be tested was 3-chloro-N-methylindole. Following the established protocol, a direct arylation competition was conducted; the result indicated a pronounced 9 : 1 preference for the chlorinated substrate. During the S_EAr competition study the non-chlorinated substrate once again reacted much faster, giving a >20 : 1 product ratio in favour of **43** (Scheme 35).



Scheme 35. Direct arylation and S_EAr competition studies for 3-chloro-N-methylindole.

The same studies were performed on the C2 chlorinated indole. Surprisingly, even though the natural arylation site was blocked on that substrate, it still reacted faster than the unsubstituted indole, leading to a 1.6 : 1 product ratio in favour of the C3 arylated species **20**. The protocol for the S_EAr experiment was altered slightly; the spectrum of the formylation competition experiment revealed the presence of numerous by-products, which hindered accurate interpretation of the results. Therefore, it was decided to carry out a Friedel-Crafts acylation instead. As with the other substrates, the non-chlorinated indole was acylated faster; the obtained product ratio was 2.3 : 1 in favour of **45** (Scheme 36).



[a] a small amount of by-product resulting from coupling of N-methylindole and 2-chloro-N-methylindole was detected

Scheme 36. Direct arylation and S_EAr competition studies for 2-chloro-N-methylindole.

2.6 Mechanistic studies: computational experiments

The activating role of the chloride group was examined through theoretical studies. A series of DFT calculations was performed on 2-chlorothiophene, 3-chloro-N-methylindole, 2-chloro-N-methylindole, and their non-chlorinated analogues. The calculations centered around two scenarios: a direct arylation pathway proceeding *via* a CMD transitions state or a Wheland intermediate (Figure 15). In relation to the CMD pathway, the activation energy ($_\Delta$E) and

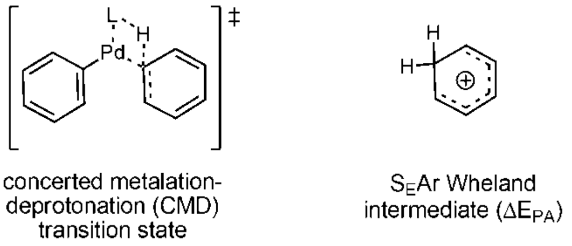
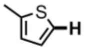
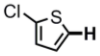
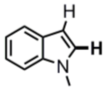
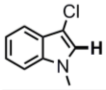
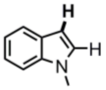
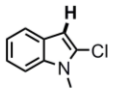


Figure 15. Two reaction pathways considered in the DFT calculations.

the Gibb's free energy of activation ($_\Delta$G) were calculated for all six species. To evaluate the impact of the chloride group on the S_EAr pathway, the tendency of each species towards an electrophilic attack was estimated by calculating the proton affinity ($_{\Delta}E_{PA}$) at the reactive sites. The phosphine ligands on Pd were modelled using PMe_3 and the pivalate ligand was approximated with an acetate. The results of the computations are summarized in Table 6. The C-H bonds under investigation are represented in bold. In accord with the experimental observations, the CMD pathway was found to be significantly lower in energy for all three chlorinated species. The proton affinity values also correlated well with the observed outcomes of the formylation/acylation competition reactions, showing a trend opposite to that seen in the CMD pathway. Clearly, based on the evidence provided by the practical and theoretical experiments, the mechanism of direct arylation for the substrates in question is incompatible with the S_EAr pathway. Although the CMD mechanism accounted well for the experimental observations, there was a need to explain just how the chloride group was able to activate the

Table 6. DFT-based direct arylation pathway analysis for chlorinated and non-chlorinated heteroarenes.

HetAr	CMD transition state						ΔE_{PA}
	E_{Dist}HetAr	$E_{Dist}PdL_n$	E_{Int}	$\Delta E^{\ddagger}$	$\Delta G^{\ddagger}$	$B_{(Pd-C)}$	
	40.7	17.8	-42.9	15.6	25.8	0.537	212.5
	37.9	17.4	-41.0	14.3	24.4	0.499	205.2
	43.3	18.5	-44.3	17.5	28.2	0.559	218.0
	38.0	17.7	-41.0	14.7	25.9	0.493	217.9
	46.1	18.9	-47.7	17.3	28.0	0.569	226.8
	43.4	18.1	-46.0	15.5	25.7	0.535	225.6

All energies expressed in kcal/mol, E_{Dist} = distortion enegry, E_{Int} = interaction energy, $B_{(Pd-C)}$ = Pd-C Mayer bond order, E_{PA} = electronic component of proton affinity at corresponding carbon, PdL_n = $Pd(Ph)(PMe_3)(OAc)$

heteroarenes towards arylation. For that purpose, a strain-activation analysis of the CMD pathway was performed (Figure 16)[43]. In this approach, the energetic cost associated with the distortion ($E_{Dist.}$) of both the heteroarene (HetAr) and the catalyst (PdL_n) from their ground state (1+2) to their transition state geometries (3+4) and the energetic gain from the electronic interaction of the two species in the CMD transition state ($E_{Int.}$) were evaluated. For each pair of substrates, the presence of a chlorine substituent resulted in a decrease in $E_{Dist.}$(HetAr), however the $E_{Dist.}$(PdL_n) remained almost unaffected by the C-Cl bond. Chlorination was also found to raise the interaction energy in the transition state. An electronic structure analysis of the covalent interactions in the CMD transition state revealed that the Pd-C(HetAr) bond order decreased in the presence of the chloro-group.

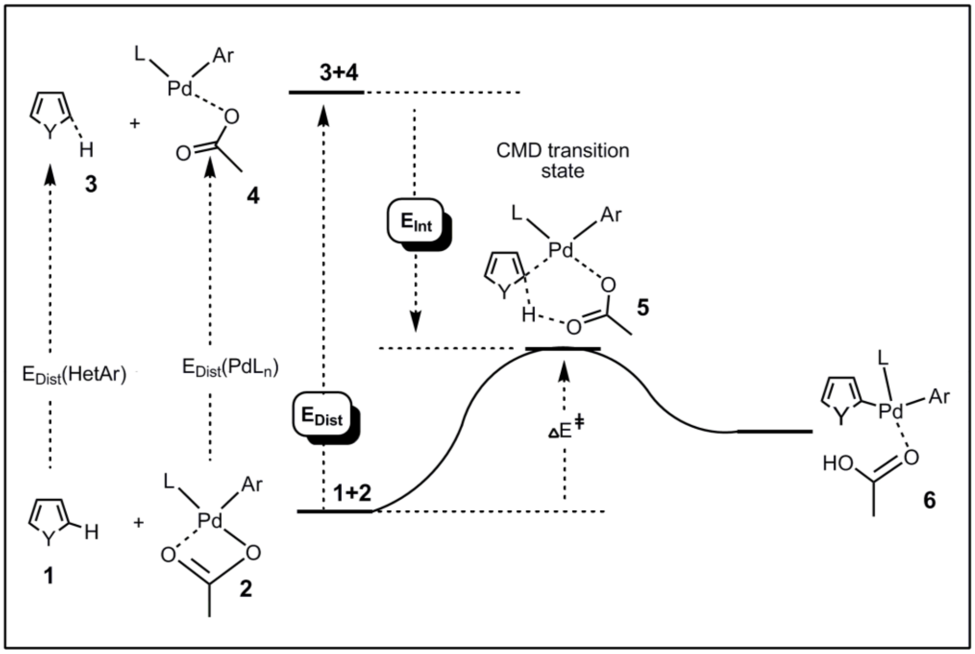


Figure 16. Strain-activation analysis of CMD-based direct arylation of heteroarenes.

The computational details gathered herein begin to shed light on the mechanism by which the chloride group activates heteroaromatics towards direct arylation under the assumption that the

CMD pathway is operative for the given heteroarenes. Since the positive influence of this blocking/activating group on $E_{Dist.}$(HetAr) outweighs its negative influence on $E_{Int.}$, the improved reactivity of the chlorinated substrates is primarily a consequence of this net beneficial effect. In a broader sense, the mechanistic studies presented in this text have yielded results that corroborate earlier claims by the Fagnou group that the CMD mechanism is not only a viable contender among other proposed direct arylarion pathways, but may be operative in more instances than previously thought. The CMD mechanism has the ability to accurately predict and explain reaction outcomes for a diverse set of aromatic substrates that might appear divergent and anomalous under the simple S_EAr paradigm. In contrast to the latter mechanism, CMD reactivity may not be governed by arene nucleophilicity alone, as shown by competition experiments and theoretical work. Moreover, the importance of carbonates, acetates, and pivalates[1,2,3,70] in direct arylation protocols may also be explained by the involvement of the CMD mechanism. Conceivably, if direct arylation reactions in general reside on a flat energetic landscape, multiple reaction pathways, including CMD and S_EAr may be accessible depending on subtle differences in substrate combinations and reaction conditions.

3. CONCLUSION

The regioselectivity in Pd(0)-catalyzed direct arylation of pyrrole, thiophene, and indole can be improved by blocking some of the reactive sites with a chloride group, leading to increased yields of the desired regioisomers. Competition experiments and computational studies show that the blocking group also activates the substrates toward arylation. Due to the activated nature of chlorinated heteroaromatics rare and sought after regioisomers, such as 3-arylthiophenes, can be obtained under mild conditions in good yields. Chlorine-bearing thiophenes arylated at C3 and C4 have the potential to undergo controlled regioregular polymerization under conditions developed in the field of polythiophene chemistry. Mechanistic studies support the hypothesis that the arylation of the substrates under investigation likely proceeds *via* the CMD transition state.

4. CLAIM TO ORIGINAL RESEARCH

The synthetic methodologies presented in this work offer a simple solution to the problem of regioselective direct arylation of heteroaromatics. This approach has not been previously disclosed in scientific literature; it can be considered complimentary to other methods and advantageous due to the possibility of using the blocking group as a synthetic handle. The use of the chloride blocking group has also been shown to have an activating effect on the substrates in question. Details can be found in the Journal of Organic Chemistry (Liégault, B.; Petrov, I.; Gorelsky, S.I.; Fagnou, K. *J. Org. Chem.*, **2010**, *75 (4)*, 1047–1060.)

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6. EXPERIMENTAL

General considerations:

^{1}H and ^{13}C NMR were recorded in $CDCl_3$ or DMSO-*d*6 (with TMS as an internal standard) using a 400 MHz spectrometer. $Pd(OAc)_2$, $P(Cy)_3H{\cdot}BF_4$ and $P(t\text{-}Bu)_2MeH{\cdot}BF_4$ were stored in a dessicator and weighed to air. All reagents were used without further purification unless otherwise specified. HPLC grade THF, Et_2O,CH_2Cl_2 and toluene were dried and purified via a solvent purification system. DMA , ^{i}PrOAc and mesitylene were stored over molecular sieves, and used without further purification.

Direct arylation procedures:

A HetAr (1.0 eq.), ArX (1.0 eq.), $Pd(OAc)_2$ (2 mol%), $P(Cy)_3H{\cdot}BF_4$ (4 mol%), K_2CO_3 (1.5 eq.), PivOH (30 mol%), DMA, 100°C, 16h.

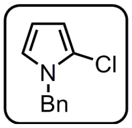
B HetAr (1.0 eq.), ArX (1.0 eq.), $Pd(OAc)_2$ (5 mol%), $P(t\text{-}Bu)_2MeH{\cdot}BF_4$ (10 mol%), Cs_2CO_3 (2 eq.), PivOH (30 mol%), mesitylene, 140°C, 24h.

C HetAr (1.5 eq.), ArX (1.0 eq.), $Pd(OAc)_2$ (5 mol%), $P(t\text{-}Bu)_2MeH{\cdot}BF_4$ (10 mol%), K_2CO_3 (2 eq.), PivOH (30 mol%), ^{i}PrOAc, 100°C, 24h.

All solid reagents were weighed into reaction vials, which were then purged with argon. Following the addition of the solvent, liquid reagents were introduced *via* a syringe.

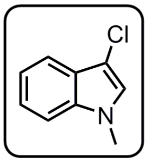
Computational details:

Density Functional Theory (DFT) calculations have been performed using the *Gaussian 03* program. In all calculations, the spin-restricted method was employed. Wave function stability calculations were carried out to confirm that the calculated wave functions corresponded to the electronic ground state. The structures of all species were optimized using the B3LYP exchange-correlation functional with the mixed basis set (DZVP on Pd and TZVP on all other atoms). The Pd catalyst was modeled with PMe_3 ligands and an acetate base. Tight SCF convergence criteria (10-8 a.u.) were used for all calculations. Harmonic frequency calculations with the analytic evaluation of force gradients (OPT = CalcAll) were used to determine the nature of the stationary points. Intrinsic reaction coordinate (IRC) calculations were used to confirm the reaction pathways through the CMD transition states (TSs). Free energies of species were evaluated at 298 K and 1 atm. Mayer bond orders were calculated using the *AOMix* program.

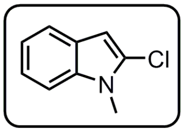


1-benzyl-2-chloropyrrole 1. To a solution of 1-benzyl-pyrrole (0.5 g, 3.4 mmol, 1 eq) in dry Et_2O (10 mL) at 0 °C under argon is added a solution of SO_2Cl_2 (0.3 mL, 3.4 mmol, 1 eq) in dry Et_2O (5 mL) dropwise. The mixture is allowed to warm up to r.t with stirring. After 15 min of stirring at r.t, the crude product is washed with saturated $NaHCO_3$, extracted with Et_2O, washed with water, dried with $MgSO_4$, concentrated under reduced pressure, and purified by silica gel chromatography to afford 0.49 g of **1** as a colorless oil in 75% yield. R_f 0.5 (petroleum ether/AcOEt 97/3); ^1H NMR (400 MHz, $CDCl_3$) δ 7.34-7.27

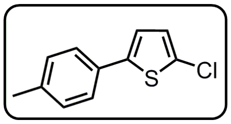
(m, 3H), 7.09 (dd, $J = 7.0$ and 0.7 Hz, 2H), 6.63 (ddd, $J = 4.1$, 0.9 and 0.9 Hz, 1H), 6.15 (ddd, $J = 5.6$, 1.2 and 1.2 Hz, 1H), 6.10 (ddd, $J = 4.1$, 1.3 and 1.3 Hz, 1H), 5.07 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.3, 128.7, 127.6, 126.8, 120.7, 116.0, 108.2, 106.8, 50.2; IR (ν_{max}) 1700, 1652, 1083, 757, 684cm^{-1}; HRMS Calcd for $C_{11}H_{10}ClN$ (M^+) 191.0502, Found 191.0506.



3-chloro-*N*-methylindole 2. *N*-methylindole (0.25 g, 1.9 mmol) is dissolved in MeCN (6 mL) and N-chlorosuccinimide (0.25 g, 1.9 mmol, 1.0 eq.) is added at once. The resulting mixture is stirred at r.t. overnight. The crude product is washed with water, extracted with EtOAc, dried with $MgSO_4$, concentrated under reduced pressure, and purified by silica gel chromatography to afford 0.19 g of **2** as a pale yellow oil in 62% yield. R_f 0.4 (petroleum ether/AcOEt 95/5); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (dt, $J = 6.0$ and 0.9 Hz, 1H), 7.30-7.24 (m, 2H), 7.17 (ddd, $J = 12.6$, 1.7, and 1.6 Hz, 1H), 6.99 (s, 1H), 3.72 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.8, 125.7, 125.2, 122.6, 119.9, 118.3, 109.4, 104.4, 32.9; IR (ν_{max}) 3125, 2941, 1465, 1361, 1324, 1240, 1109, 967, 738 cm^{-1}; HRMS Calcd for C_9H_8ClN (M^+) 165.0345, Found 165.0331.

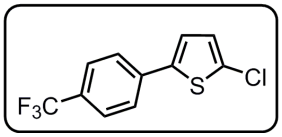


2-chloro-*N*-methylindole 3. N-methyloxindole (0.3 g, 2.0 mmol) was weighed into a flask, which was then purged with argon. Dry DCM (1.0 mL) was added and the solution cooled to 0 °C with stirring. $POCl_3$ (1.2 mL, 12 mmol, 6.0 eq) was added dropwise via a syringe. The resulting mixture was heated to reflux and allowed to stir for 1.5 h. Afterwards, the mixture was transferred dropwise into a beaker of crushed ice and aqueous $NaHCO_3$ with a pipette and allowed to stir for 10 min. The crude mixture was washed with water, the aqueous phase was extracted with DCM. The organic extracts were combined, dried over $MgSO_4$, concentrated under reduced pressure, and purified by silica gel chromatography to afford 0.13 g of **3** as a white solid in 38% yield (91% BRSM). R_f 0.6 (petroleum ether/toluene 90/10); mp 63-64 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (dt, J = 7.9 and 1.0 Hz, 1H), 7.25 (br d, J = 8.8 Hz, 1H), 7.20 (ddd, J = 6.9, 6.9, 1.2 Hz, 1H), 7.11 (ddd, J = 6.9, 6.9, 1.2 Hz, 1H), 6.45 (d, J = 0.7 Hz, 1H), 3.72 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.1, 126.9, 126.0, 121.6, 120.2, 119.8, 109.2, 99.6, 29.7; IR (ν_{max}) 3129, 1504, 1469, 1328, 1230, 1158, 773 cm^{-1}; HRMS Calcd for C_9H_8ClN (M^+) 165.0345, Found 165.0360.

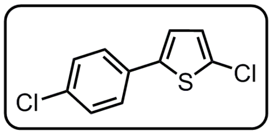


2-chloro-5-(*p*-tolyl)thiophene 4. Synthesized according to general procedure **A**. Pale yellow solid; mp 83-84 °C; R_f 0.7 (100% petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (dt, J = 8.1 and 2.1 Hz, 2H), 7.17 (dt, J = 7.9 and 2.1 Hz, 2H), 7.01 (d, J = 3.9 Hz, 1H), 6.86 (d, J = 3.9 Hz, 1H), 2.36 (s, 3H); ^{13}C NMR

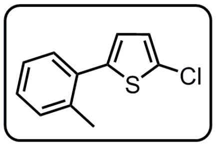
(100 MHz, $CDCl_3$) δ 143.1, 137.8, 130.9, 129.6, 128.5, 127.0, 125.4, 121.7, 21.2; IR (ν_{max}) 1502, 1439, 1214, 815, 789, 751 cm^{-1}; HRMS Calcd for $C_{11}H_9ClS$ (M^+) 208.0113, Found 208.0103.



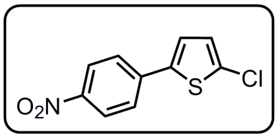
2-chloro-5-(4-trifluoromethyl-phenyl)thiophene 5. Synthesized according to general procedure **A**. Pale yellow solid; mp 82-83 °C; R_f 0.6 (petroleum ether/AcOEt 95/5); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64-7.59 (m, 4H), 7.16 (d, J = 3.9 Hz, 1H), 6.93 (d, J = 3.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.0, 137.0, 130.8, 129.8, 129.4, 127.4, 126.0 (q, J_{CF} = 3.9 Hz), 125.8, 123.7; IR (ν_{max}) 2933, 1616, 1438, 1326, 1132, 1113, 907 cm^{-1}; HRMS Calcd for $C_{11}H_6ClF_3S$ (M^+) 261.9831, Found 261.9836.



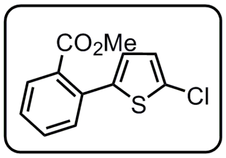
2-chloro-5-(4-chlorophenyl)thiophene 6. Synthesized according to general procedure **A**. Yellow solid; mp 75-76 °C; R_f 0.7 (petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (dt, J = 8.8 and 2.4 Hz, 2H), 7.34 (dt, J = 8.8 and 2.4 Hz, 2H), 7.04 (d, J = 3.9 Hz, 1H), 6.88 (d, J = 3.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.5, 133.6, 132.2, 129.6, 129.2, 127.2, 126.7, 122.6; IR (ν_{max}) 3093, 1491, 1438, 1096, 1006, 900, 826 cm^{-1}; HRMS Calcd for $C_{10}H_6Cl_2S$ (M^+) 227.9567, Found 227.9552.



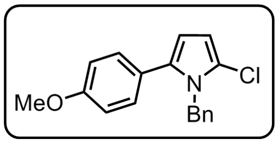
2-chloro-5-(*o*-tolyl)thiophene 7. Synthesized according to general procedure **A**. Yellow solid; mp 85-86 °C; R_f 0.6 (100% petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (br d, $J = 6.9$ Hz, 1H), 7.25 (dd, $J = 5.1$ and 1.3 Hz, 2H), 7.23-7.18 (m, 1H), 6.89 (d, $J = 3.8$ Hz, 1H), 6.81 (d, $J = 3.8$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.8, 136.1, 133.3, 130.8, 130.3, 129.3, 128.2, 126.2, 126.0, 125.6, 21.0; IR (ν_{max}) 2926, 1485, 1456, 1002, 801, 756 cm^{-1}; HRMS Calcd for $C_{11}H_9ClS$ (M^+) 208.0113, Found 208.0103.



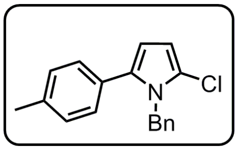
2-chloro-5-(4-nitrophenyl)thiophene 8. Synthesized according to general procedure **A**. Bright yellow solid; mp 114-115 °C; R_f 0.5(petroleum ether/AcOEt 95/5); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (dt, $J = 9.0$ and 2.5 Hz, 2H), 7.64 (dt, $J = 9.0$ and 2.5 Hz, 2H), 7.25 (d, $J = 4.0$ Hz, 1H), 6.97 (d, $J = 4.0$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.8, 140.0, 139.7, 132.5, 127.8, 125.6, 125.0, 124.5; IR (ν_{max}) 1589, 1509, 1418, 1336, 842, 792, 748 cm^{-1}; HRMS Calcd for $C_{10}H_6ClNO_2S$ (M^+) 238.9808, Found 238.9811.



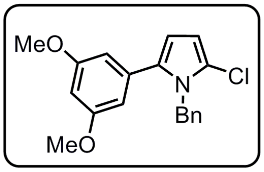
Methyl 2-(5-chlorothiophen-2-yl)benzoate 9. Synthesized according to general procedure **A**. Green oil; R_f 0.7 (petroleum ether/AcOEt 90/10); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (dt, $J = 6.8$ and 1.0 Hz, 1H), 7.50 (td, $J = 6.6$ and 1.5 Hz, 1H), 7.43-7.49 (m, 2H), 6.88 (d, $J = 3.8$ Hz, 1H), 6.80 (d, $J = 3.8$ Hz, 1H), 3.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5, 140.5, 133.3, 131.4, 131.1, 131.0, 129.6, 128.1, 126.2, 125.5, 52.2; IR (ν_{max}) 2954, 1727, 1432, 1292, 1254, 1162, 1003, 758 cm^{-1}; HRMS Calcd for $C_{12}H_9ClO_2S$ (M^+) 252.0012, Found 251.9966.



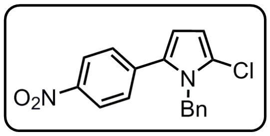
1-benzyl-2-chloro-5-(4-methoxyphenyl)-1*H*-pyrrole 10. Synthesized according to general procedure **A**. White solid; mp 87-88°C; R_f 0.5 (1:9 Et_2O : petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.21 (m, 3H), 7.16 (br d, $J = 8.8$ Hz, 2H), 6.93 (br d, $J = 7.1$ Hz, 2H), 6.83 (br d, $J = 8.8$ Hz, 2H), 6.18 (dd, $J = 5.7$ and 3.7 Hz, 2H), 5.15 (s, 2H), 3.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 138.2, 134.4, 130.2, 128.6, 127.1, 125.8, 125.5, 117.0, 113.9, 107.9, 106.8, 55.3, 47.8; IR (ν_{max}) 1699, 1523, 1448, 824,723cm^{-1}; HRMS Calcd for $C_{18}H_{16}ClNO$ (M^+) 297.0920, Found 297.0914.



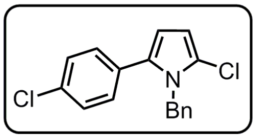
1-benzyl-2-chloro-5-(*p*-tolyl)pyrrole 11. Synthesized according to general procedure **A**. Clear oil; R_f 0.7 (petroleum ether/Et_2O 97/3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.21 (m, 3H), 7.15-7.09 (m, 4H), 6.92 (d, $J = 8.0$ Hz, 2H), 6.21 (dd $J = 3.8$ and 1.1 Hz, 1H), 6.20 (dd $J = 3.8$ and 1.1 Hz, 1H), 5.16 (s, 2H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.2, 137.2, 134.7, 130.1, 129.1, 128.7, 128.6, 127.1, 125.8, 117.4, 108.2, 106.9, 47.9, 21.1; IR (ν_{max}) 3083, 2927, 1496, 1453, 1354, 1304, 820, 757, 726, 684 cm^{-1}; HRMS Calcd for $C_{18}H_{16}ClN$ (M^+) 281.0971, Found 281.0949.



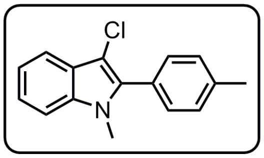
1-benzyl-2-chloro-5-(3,5-dimethoxyphenyl)pyrrole 12. Synthesized according to general procedure **A**. White solid; mp 106-107 °C; R_f 0.4 (petroleum ether/Et_2O 90/10); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.29 (m, 2H), 7.25-7.21 (m, 1H), 6.99 (br d, J = 7.6 Hz, 2H), 6.38 (br s, 3H), 6.26 (dd, J = 3.3 and 0.5 Hz, 1H), 6.21 (dd, J = 3.3 and 0.5 Hz, 1H), 5.22 (s, 2H), 3.60 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.6, 138.3, 134.7, 128.7, 127.1, 125.8, 118.0, 109.8, 108.5, 106.9, 106.5, 100.1, 55.1, 48.1; IR (ν_{max}) 2931, 1592, 1468, 1277, 1204, 1155, 1056, 834, 761, 720 cm^{-1}; HRMS Calcd for $C_{19}H_{18}ClNO_2$ (M^+) 327.1026, Found 327.1014.



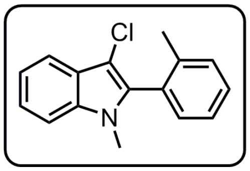
1-benzyl-2-chloro-5-(4-nitrophenyl)pyrrole 13. Synthesized according to general procedure **A**. Green solid; mp 112-113 °C; R_f 0.4 (petroleum ether/AcOEt 85/15); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (dt, J = 9.0 and 2.4 Hz, 2H), 7.39 (dt, J = 9.0 and 2.4 Hz, 2H), 7.35-7.29 (m, 3H), 6.95 (br d, J = 6.8 Hz, 2H), 6.43 (d, J = 3.9 Hz, 1H), 6.29 (d, J = 3.9 Hz, 1H), 5.25 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.4, 139.1, 137.2, 132.4, 128.9, 128.3, 127.6, 125.6, 124.0, 120.8, 111.1, 108.1, 48.3; IR (ν_{max}) 1589, 1525, 1448, 1339, 858, 744, 724, 687 cm^{-1}; HRMS Calcd for $C_{17}H_{13}ClN_2O_2$ (M^+) 312.0666, Found 312.0645.



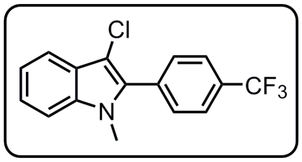
1-benzyl-2-chloro-5-(4-chlorophenyl)pyrrole 14. Synthesized according to general procedure **A**. Clear oil; R_f 0.5 (petroleum ether/toluene 90/10); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.23 (m, 5H), 7.15 (dt, $J = 8.6$ and 2.4 Hz, 2H), 6.91 (br d, $J = 7.0$ Hz, 2H), 6.23 (d, $J = 3.8$ Hz, 1H), 6.21 (d, $J = 3.8$ Hz, 1H), 5.15 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.8, 133.4, 133.3, 131.4, 129.9, 128.7, 128.6, 127.3, 125.7, 118.2, 108.9, 107.2, 47.9; IR (ν_{max}) 1489, 1448, 1304, 1096, 1012, 838, 754, 724, 694 cm^{-1}; HRMS Calcd for $C_{17}H_{13}Cl_2N$ (M^+) 301.0425, Found 301.0427.



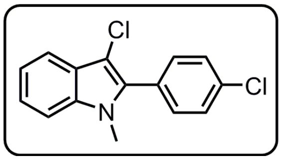
3-chloro-*N*-methyl-2-(*p*-tolyl)indole 15. Synthesized according to Conditions **A**. Orange solid; mp 94-95 °C; R_f 0.5 (petroleum ether/EtOAc 95/5); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (dt, $J = 7.8$ and 0.8 Hz, 1H), 7.40 (dd, $J = 8.1$ and 1.7 Hz, 2H), 7.33 (m, 3H), 7.28 (td, $J = 6.9$ and 1.2 Hz, 1H), 7.21 (td, $J = 6.9$ and 1.2 Hz, 1H), 3.65 (s, 3H), 2.42 (s, 3H) ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.6, 136.3, 136.1, 130.4, 129.2, 126.8, 125.6, 122.6, 120.3, 118.2, 109.6, 103.3, 31.4, 21.4; IR (ν_{max}) 2930, 2860, 1463, 1358, 1233, 1099, 968, 740 cm^{-1}; HRMS Calcd for $C_{16}H_{14}ClN$ (M^+) 255.0815, Found 255.0823.



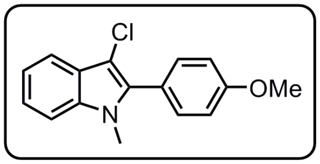
3-chloro-*N*-methyl-2-(*o*-tolyl)indole 16. Synthesized according to general procedure **A**. Thick yellow oil; R_f 0.7 (petroleum ether/AcOEt 95/5); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.67 (dt, J = 7.8 and 0.8 Hz, 1H), 7.43-7.36 (m, 3H), 7.34-7.27 (m, 3H), 7.23 (td, J = 7.9 and 1.0 Hz, 1H), 3.50 (s, 3H), 2.19 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 138.8, 136.0, 135.8, 131.3, 130.2, 129.5, 129.4, 125.8, 125.4, 122.4, 120.2, 118.1, 109.6, 103.7, 30.7, 19.7 ; IR ($\nu_{\max}$) 2934, 2854, 1463, 1352, 1234, 1099, 975, 740 cm^{-1}; HRMS Calcd for $C_{16}H_{14}ClN$ (M$^+$) 255.0815, Found 255.0823.



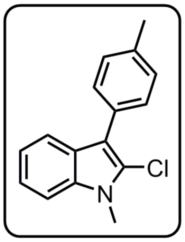
3-chloro-*N*-methyl-2-(*p*-trifluoromethylphenyl)indole 17. Synthesized according to general procedure **A**. Yellow solid; mp 80-81 °C; R_f 0.6 (petroleum ether/toluene 70/30); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.77 (d, J = 8.1 Hz, 2H), 7.68-7.63 (m, 3H), 7.36 (br d, J = 7.9, 1H), 7.33 (td, J = 6.6 and 1.1 Hz, 1H), 7.24 (td, J = 6.6 and 1.1 Hz, 1H), 3.66 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 136.5, 134.5, 133.4 (q, J_{CF} = 1 Hz), 130.8, 130.4 (q, J_{CF} = 33 Hz), 128.2, 125.5 (q, J_{CF} = 4 Hz), 124.0 (q, J_{CF} = 272 Hz), 123.5, 120.7, 118.6, 109.8, 104.5, 31.6; IR ($\nu_{\max}$) 1609, 1465, 1323, 1167, 1127, 1108, 1070, 1017, 853, 739 cm^{-1}; HRMS Calcd for $C_{16}H_{11}ClF_3N$ (M$^+$) 309.0532, Found 309.0511.



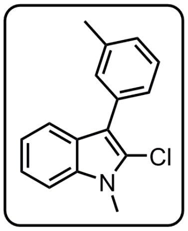
3-chloro-2-(*p*-chlorophenyl)-1-methylindole 18. Synthesized according to general procedure **A**. Yellow solid; mp 87-88 °C; R_f 0.5 (petroleum ether/AcOEt 95/5); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (dt, J = 7.8 and 1.0 Hz, 1H), 7.50 (dt, J = 8.7 and 2.0 Hz, 2H), 7.45 (dt, J = 8.7 and 2.0 Hz, 2H), 7.36 (br d, J = 8.1, 1H), 7.32 (td, J = 6.8 and 1.2 Hz, 1H), 7.23 (td, J = 6.9 and 1.2 Hz, 1H), 3.67 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.3, 134.7, 131.8, 128.8, 128.2, 125.5, 123.1, 122.6, 120.5, 119.9, 118.4, 109.7, 31.5; IR (ν_{max}) 2911, 1464, 1324, 1215, 1092, 1015, 958 cm^{-1}; HRMS Calcd for $C_{15}H_{11}Cl_2N$ (M^+) 275.0269, Found 275.0281.



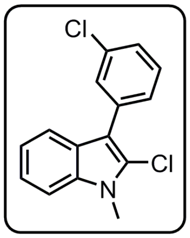
3-chloro-2-(4-methoxyphenyl)-*N*-methylindole 19. Synthesized according to general procedure **A**. White solid; mp 108-109 °C; R_f 0.3 (petroleum ether/Et_2O 90/10); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, J = 7.9 Hz, 1H), 7.44 (d, J = 8.7 Hz, 2H), 7.35 (d, J = 8.2 Hz, 1H), 7.29 (t, J = 6.9 Hz, 1H), 7.21 (t, J = 7.0 Hz, 1H), 7.05 (d, J = 8.7 Hz, 2H), 3.89 (s, 3H), 3.66 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.8, 136.1, 136.0, 131.8, 125.6, 122.6, 121.9, 120.2, 118.1, 114.0, 109.6, 103.1, 55.3, 31.4; IR (ν_{max}) 2935, 1609, 1498, 1465, 1250, 1176, 1026, 838, 740 cm^{-1}; HRMS Calcd for $C_{16}H_{14}ClNO$ (M^+) 271.0764, Found 271.0772.



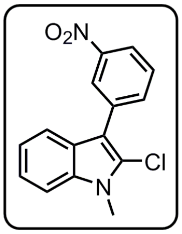
2-chloro-3-(*p*-tolyl)-1-methylindole 20. Synthesized according to general procedure **A**. Clear oil; R_f 0.5 (petroleum ether/toluene 80/20); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, J = 8.0 Hz, 1H), 7.53 (d, J = 8.1 Hz, 2H), 7.32-7.24 (m, J = 8.7, 3H), 7.15 (ddd, J = 8.0, 7.0 and 1.0 Hz, 1H), 7.32 (td, J = 6.8 and 1.2 Hz, 1H), 3.80 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.2, 135.7, 130.3, 129.2, 129.1, 126.0, 123.1, 122.2, 120.4, 119.1, 112.8, 109.2, 29.9, 21.3; IR (ν_{max}) 2922, 1546, 1465, 1370, 1084, 814, 740 cm^{-1}; HRMS Calcd for $C_{16}H_{14}ClN$ (M^+) 255.0815, Found 255.0827.



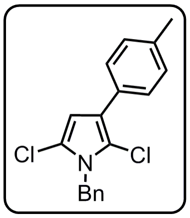
2-chloro-3-(*m*-tolyl)-1-methylindole 21. Synthesized according to general procedure **A**. Clear oil; R_f 0.6 (petroleum ether/EtOAc 95/5); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (dt, J = 7.9 and 0.9 Hz, 1H), 7.44 (br d, J = 8.8 Hz, 2H), 7.38 (t, J = 7.5 Hz, 1H), 7.31 (dd, J = 8.1 and 0.9 Hz, 1H), 7.26 (td, J = 6.9 and 1.2 Hz, 1H), 7.17-7.13 (m, 2H), 3.80 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.0, 135.7, 133.2, 129.9, 128.4, 127.3, 126.4, 126.0, 123.3, 122.2, 120.4, 119.1, 112.9, 109.2, 29.9, 21.6; IR (ν_{max}) 3120, 1323, 1240, 1159, 1009, 966, 735 cm^{-1}; HRMS Calcd for $C_{16}H_{14}ClN$ (M^+) 255.0815, Found 255.0827.



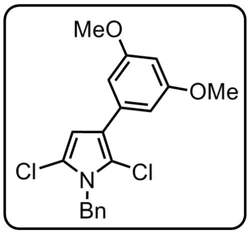
2-chloro-3-(3-chlorophenyl)-1-methylindole 22. Synthesized according to general procedure **A**. White solid; mp 87-88 °C; R_f 0.3 (petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, $J = 7.6$ Hz, 1H), 7.63 (d, $J = 1.4$ Hz, 1H), 7.53 (dd, $J = 7.7$ and 0.9 Hz, 1H), 7.40 (t, $J = 7.9$ Hz, 1H), 7.34-7.26 (m, 3H), 7.18 (t, $J = 7.2$ Hz, 1H), 3.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.7, 135.2, 134.3, 129.7, 129.1, 127.3, 126.5, 125.7, 123.7, 122.5, 120.8, 118.8, 111.6, 109.3, 30.0; IR (ν_{max}) 3062, 1600, 1470, 1360, 1253, 1083, 886 cm^{-1}; HRMS Calcd for $C_{15}H_{11}Cl_2N$ (M^+) 275.0269, Found 275.0279.



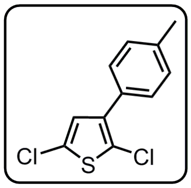
2-chloro-3-(3-nitrophenyl)-1-methylindole 23. Synthesized according to general procedure **A**. Yellow solid; mp 134-135 °C; R_f 0.4 (petroleum ether/Et_2O 90/10); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (t, $J = 1.9$ Hz, 1H), 8.18 (ddd, $J = 8.2$, 2.2, 0.9 Hz, 1H), 7.97 (ddd, $J = 7.7$, 1.5, 1.2 Hz, 1H), 7.69 (dt, $J = 8.0$ and 0.9 Hz, 1H), 7.63 (t, $J = 8.0$ Hz, 1H), 7.40 (br d, $J = 8.1$ Hz, 1H), 7.32 (dt, $J = 6.9$ and 1.2 Hz, 1H), 7.22 (ddd, $J = 8.0$, 6.9, 1.2 Hz, 1H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.6, 135.8, 135.3, 135.0, 129.4, 125.4, 124.2, 123.8, 122.9, 121.2. 121.1, 118.4, 110.7, 109.6, 30.2; IR (ν_{max}) 2939, 1539, 1526, 1347, 803, 736 cm^{-1}; HRMS Calcd for $C_{15}H_{11}ClN_2O_2$ (M^+) 286.0509, Found 286.0500.



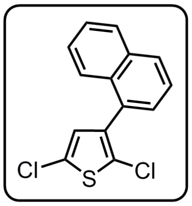
1-benzyl-2,5-dichloro-3-*p*-tolyl-1*H*-pyrrole 24. Synthesized according to the general procedure **B**. White solid; mp 109-110°C; R_f 0.5 (2:8 toluene : petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (br d, $J = 8.1$ Hz, 2H), 7.35-7.26 (m, 3H), 7.19 (br d, $J = 7.9$ Hz, 2H), 7.15 (br d, $J = 7.2$ Hz, 2H), 6.34 (s, 1H), 5.23 (s, 2H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.5, 136.2, 130.8, 129.1, 128.7, 127.6, 127.1, 126.6, 120.8, 115.8, 111.8, 106.8, 47.8, 21.2; IR (ν_{max}) 2910, 1726, 1412, 1323, 1135, 1096, 900 cm^{-1}; HRMS Calcd for $C_{18}H_{15}Cl_2N$ (M^+) 315.0582, Found 315.0571.



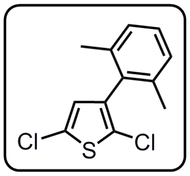
1-benzyl-2,5-dichloro-(3,5-dimethoxyphenyl)-1*H*-pyrrole 25. Synthesized according to the general procedure **B**. White solid; mp 115-116 °C; R_f 0.4 (1:9 Et_2O : petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.32 (m, 2H), 7.29 (br d, $J = 7.2$ Hz, 1H), 7.15 (br d, $J = 6.9$ Hz, 2H), 6.75 (d, $J = 2.3$ Hz, 2H), 6.39 (t, $J = 2.3$ Hz, 1H), 6.36 (s, 1H), 5.24 (s, 2H), 3.81 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.8, 136.3, 135.5, 128.7, 127.6, 126.6, 120.7, 115.9, 112.3, 106.9, 105.4, 98.8, 55.3, 47.8; IR (ν_{max}) 2930, 1830, 1372, 1323, 1120, 1096, 907, 750 cm^{-1}; HRMS Calcd for $C_{19}H_{17}Cl_2NO_2$ (M^+) 361.0636, Found 361.0625.



2,5-dichloro-3-*p*-tolylthiophene 26. Synthesized according to the general procedure **C**. White solid; mp 87-88 °C; R_f 0.8 (petroleum ether); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.40 (br d, J = 8.1 Hz, 2H), 7.23 (br d, J = 7.9 Hz, 2H), 6.88 (s, 1H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 138.1, 137.9, 130.5, 129.3, 128.2, 127.5, 126.2, 121.2, 21.3; IR ($\nu_{\max}$) 2820, 1712, 1438, 1323, 1237, 1113, 1096, 907 cm^{-1}; HRMS Calcd for $C_{11}H_8Cl_2S$ (M$^+$) 241.9724, Found 241.9731.

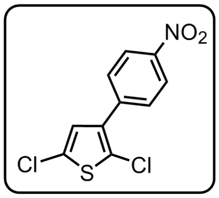


2,5-dichloro-3-(naphthalen-1-yl)thiophene 27. Synthesized according to the general procedure **C**. White solid; mp 110-111 °C; R_f 0.6 (petroleum ether); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.91-7.88 (m, 2H), 7.71 (br d, J = 7.8 Hz, 1H), 7.53-7.48 (m, 3H), 7.43 (dd, J = 7.0 and 1.2 Hz, 1H), 6.88 (s, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 137.5, 133.7, 131.5, 131.1, 128.9, 128.7, 128.4, 127.8, 126.5, 126.2, 126.1, 125.5, 125.2, 124.0; IR ($\nu_{\max}$) 2913, 1685, 1335, 1323, 1226, 1100, 1068, 750 cm^{-1}; HRMS Calcd for $C_{14}H_8Cl_2S$ (M$^+$) 277.9724, Found 277.9732.

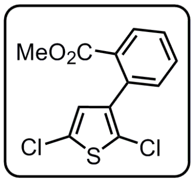


2,5-dichloro-3-(2,6-dimethylphenyl)thiophene 28. Synthesized according to the general procedure **C**. White solid; mp 89-90 °C; R_f 0.65 (petroleum ether);

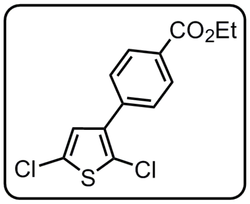
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (br t, J = 8.1 Hz, 1H), 7.09 (br d, J = 7.6 Hz, 2H), 6.62 (s, 1H), 2.10 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.1, 137.2, 132.8, 128.3, 127.3, 127.2, 126.4, 123.1, 20.2; IR (ν_{max}) 2831, 1711, 1425, 1235, 1115, 1096, 912 cm^{-1}; HRMS Calcd for $C_{12}H_{10}Cl_2S$ (M^+) 255.9880, Found 255.9864.



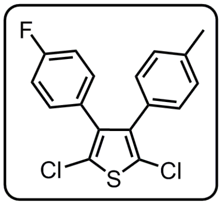
2,5-dichloro-3-(4-nitrophenyl)thiophene 29. Synthesized according to the general procedure **C**. Yellow solid; mp 121-122 °C; R_f 0.7 (1.5:8.5 Et_2O : petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (br d, J = 8.9 Hz, 2H), 7.70 (br d, J = 8.9 Hz, 2H), 6.95 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.2, 139.5, 135.8, 129.2, 127.6, 126.8, 124.0, 123.9; IR (ν_{max}) 2959, 2931, 2854, 1529, 1348, 1101, 736 cm^{-1}; HRMS Calcd for $C_{10}H_5Cl_2NO_2S$ (M^+) 272.9418, Found 272.9413.



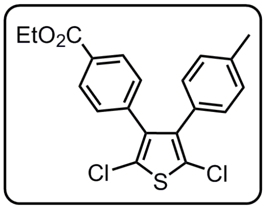
Methyl- 2-(2,5-dichlorothiophen-3-yl)benzoate 30. Synthesized according to the general procedure **C**. White solid; mp 82-83 °C; R_f 0.5 (0.5:9.5 Et_2O : petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (dd, J = 7.8 and 1.1 Hz, 1H), 7.56 (td, J = 7.6 and 1.5 Hz, 1H), 7.46 (td, J = 7.7 and 1.4 Hz, 1H), 7.32 (dd, J = 7.7 and 1.3 Hz, 1H), 6.76 (s, 1H), 3.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 138.0, 134.1, 131.9, 131.2, 130.6, 130.5, 128.4, 127.7, 125.8, 122.5, 52.3; IR (ν_{max}) 1714, 1602, 1273, 1153, 1103 cm^{-1}; HRMS Calcd for $C_{12}H_8Cl_2O_2S$ (M^+) 285.9622, Found 285.9612.



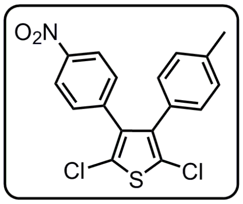
Ethyl 4-(2,5-dichlorothiophen-3-yl)benzoate 31. Synthesized according to the general procedure **C**. White solid; mp 107-108 °C; R_f 0.4 (1.5 : 8.5 Et_2O : petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (br d, J = 8.6 Hz, 2H), 7.59 (br d, J = 8.6 Hz, 2H), 6.93 (s, 1H), 4.40 (q, J = 7.1 Hz, 2H), 1.41 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 137.5, 137.1, 129.9, 129.8, 127.2, 126.9, 122.9, 61.1, 14.3; IR (ν_{max}) 1718, 1272, 1102, 1024, 770 cm^{-1}; HRMS Calcd for $C_{13}H_{10}Cl_2O_2S$ (M^+) 299.9779, Found 299.9754.



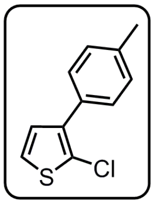
2,5-dichloro-3-(4-fluorophenyl)-4-*p*-tolylthiophene 32. Synthesized according to the general procedure **C**. White solid; mp 123-124 °C; R_f 0.5 (petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08-7.03 (m, 4H), 6.97-6.92 (m, 4H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2 (d, J_{CF} = 247 Hz), 141.3, 138.8, 138.1, 133.3, 130.3 (d, J_{CF} = 3.3 Hz), 130.2 (d, J_{CF} = 8.1 Hz), 128.9 (d, J_{CF} = 6.8 Hz), 126.2, 123.7, 123.6, 122.6, 115.4 (d, J_{CF} = 21.6 Hz), 21.4; IR (ν_{max}) 2922, 1507, 1448, 1225, 1162, 1142, 837, 745 cm^{-1}; HRMS Calcd for $C_{17}H_{11}Cl_2FS$ (M^+) 335.9943, Found 335.9959.



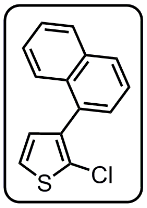
Ethyl 4-(2,5-dichloro-4-*p*-tolylthiophen-3-yl)benzoate 33. Synthesized according to the general procedure **C**. White solid; mp 117-118 °C; R_f 0.55 (0.5 : 9.5 Et_2O : petroleum ether); ^1H NMR (400 MHz, $CDCl_3$) δ 7.94 (br d, J = 8.6 Hz, 2H), 7.17 (br d, J = 8.6 Hz, 2H), 7.06 (br d, J = 7.9 Hz, 2H), 6.95 (br d, J = 8.1 Hz, 2H), 4.36 (q, J = 7.1 Hz, 2H), 2.39 (s, 3H), 1.38 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 138.7, 138.0, 137.9, 137.7, 130.2, 129.9, 129.8, 129.5, 129.3, 128.9, 123.4, 122.9, 61.0, 21.1, 14.3; IR (ν_{max}) 2930, 1718, 1304, 1102, 1095, 750 cm^{-1}; HRMS Calcd for $C_{20}H_{16}Cl_2O_2S$ (M^+) 390.0248, Found 390.0231.



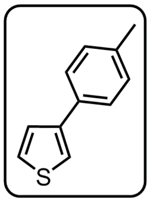
2,5-dichloro-3-(4-nitrophenyl)-4-p-tolylthiophene 34. Synthesized according to the general procedure **C**. Yellow solid; mp 129-130 °C; R_f 0.4 (1.5 : 8.5 Et_2O : petroleum ether); ^1H NMR (400 MHz, $CDCl_3$) δ 8.12 (br d, J = 8.9 Hz, 2H), 7.27 (br d, J = 8.9 Hz, 2H), 7.08 (br d, J = 8.4 Hz, 2H), 6.94 (br d, J = 8.2 Hz, 2H) 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.3, 133.8, 133.1, 128.3, 125.2, 125.1, 123.9, 121.2, 118.7, 117.6, 110.6, 110.3, 16.4; IR (ν_{max}) 2959, 2931, 2854, 1529, 1348, 1101, 736 cm^{-1}; HRMS Calcd for $C_{17}H_{11}Cl_2NO_2S$ (M^+) 362.9888, Found 362.9873.



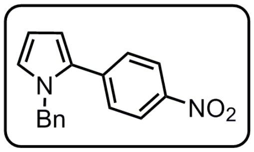
2-chloro-3-*p*-tolylthiophene 35. Synthesized according to the general procedure **C**. White solid; mp 84-85 °C; R_f 0.6 (petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (br d, J = 8.1 Hz, 2H), 7.24 (br d, J = 7.9 Hz, 2H), 7.12 (d, J = 5.7 Hz, 1H), 7.04 (d, J = 5.7 Hz, 1H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.2, 137.4, 131.3, 129.2, 128.6, 128.4, 124.4, 122.5, 21.2; IR (ν_{max}) 2957, 2929, 2859, 1510, 811 cm^{-1}; HRMS Calcd for $C_{11}H_9ClS$ (M^+) 208.0113, Found 208.0110.



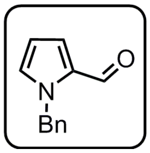
2-chloro-3-(naphthalen-1-yl)thiophene 36. Synthesized according to the general procedure **C**. White solid; mp 109-110 °C; R_f 0.5 (petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91-7.88 (m, 2H), 7.71 (br d, J = 8.2 Hz, 1H), 7.55-7.44 (m, 4H), 7.23 (d, J = 5.7 Hz, 1H), 7.03 (d, J = 5.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.6, 133.7, 132.1, 131.7, 129.9, 128.5, 128.4, 127.8, 127.0, 126.2, 125.9, 125.8, 125.2, 122.5; IR (ν_{max}) 2955, 2932, 2856, 1599, 1580, 1489, 1462, 1286,1049, 778 cm^{-1}; HRMS Calcd for $C_{14}H_9ClS$ (M^+) 244.0113, Found 244.0102.



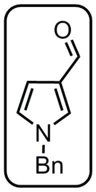
3-*p*-tolylthiophene 37. Synthesized according to the general procedure **C**. White solid; mp 89-90 °C; R_f 0.5 (petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (br d, J = 8.6 Hz, 2H), 7.40 (t, J = 2.1 Hz, 1H), 7.37 (d, J = 2.2 Hz, 2H), 7.20 (br d, J = 7.9 Hz, 2H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.3, 136.9, 133.1, 129.5, 126.3, 126.0, 119.6, 21.1; IR (ν_{max}) 2856, 1599, 1580, 1489, 1462, 1286, 1049, 778 cm^{-1}; HRMS Calcd for $C_{11}H_{10}S$ (M^+) 174.0503, Found 174.0509.



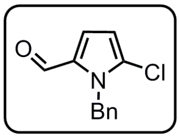
1-Benzyl-2-(4-nitrophenyl)pyrrole 38. Synthesized according to general procedure **A**. Yellow oil; R_f 0.2 (petroleum ether/EtOAc 95/5); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (ddd, J = 8.9 and 2.1 Hz, 2H), 7.44 (ddd, J = 8.9 and 2.1 Hz, 2H)7.33-7.24 (m, 3H), 6.99 (br d, J = 6.8 Hz, 2H), 6.86 (dd, J = 2.6 and 1.8 Hz, 1H), 6.45 (dd, J = 3.7 and 1.8 Hz, 1H), 6.32 (dd, J = 3.7 and 2.6 Hz, 1H), 5.21 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.1, 139.6, 137.9, 132.5, 128.9, 128.3, 127.7, 126.1, 125.8, 123.8, 111.6, 109.4, 51.1; IR (ν_{max}) 1590, 1519, 1333, 1107, 858, 717, 687 cm^{-1}; HRMS Calcd for $C_{17}H_{14}N_2O_2$ (M^+) 278.1055, Found 278.1060.



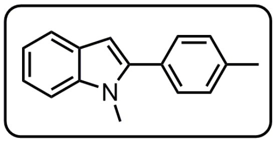
1-Benzylpyrrole-2-carbaldehyde 39. To a solution of N-benzylpyrrole (150 μL, 1 mmol) in DMF (78 μL, 1 mmol, 1 equiv.) at 0 °C under argon is added $POCl_3$ (92 μL, 1 mmol, 1 equiv.) dropwise. The mixture is stirred 20 min at r.t., 2 h under reflux (100 °C), cooled down to r.t., then immerged in an crushed ice/water bath. The resulting solution is neutralized by addition of powdered NaOAc, and the crude product is extracted with CH_2Cl_2, dried with $MgSO_4$, concentrated under reduced pressure, and purified by silica gel chromatography to afford 165 mg of **39** as a yellow oil in 89% yield. R_f 0.6 (petroleum ether/ethyl acetate 80/20). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.56 (s, 1H), 7.33-7.24 (m, 3H), 7.14 (br d, J = 7.0 Hz, 2H), 6.97 (d, J = 3.9 Hz, 2H), 6.27 (t, J = 3.2 Hz, 1H), 5.56 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.5, 137.5, 131.5, 131.3, 128.7, 127.7, 127.5, 124.8, 110.1, 51.9; IR (ν_{max}) 2927, 1593, 1464, 1422, 1205, 1156, 1065, 1039, 741 cm^{-1}; HRMS Calcd for $C_{12}H_{11}NO$ (M^+) 185.0841, Found 185.0825.



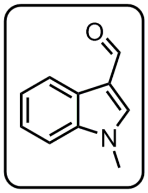
1-Benzylpyrrole-3-carbaldehyde 40. To a solution of *N*-benzylpyrrole (150 μL, 1 mmol) in DMF (78 μL, 1 mmol, 1 equiv.) at 0 °C under argon is added $POCl_3$ (92 μL, 1 mmol, 1 equiv.) dropwise. The mixture is stirred 20 min at r.t., 2 h under reflux (100 °C), cooled down to r.t., then immersed in an crushed ice/water bath. The resulting solution is neutralized by addition of powdered NaOAc, and the crude product is extracted with CH_2Cl_2, dried with $MgSO_4$, concentrated under reduced pressure, and purified by silica gel chromatography to afford 27.5 mg of **40** as a yellow oil in 15% yield. R_f 0.19 (petroleum ether/ethyl acetate 80/20). ^{1}H NMR (400 MHz, CDCl$_3$) δ 9.74 (s, 1H), 7.39-7.30 (m, 4H), 7.16 (br d, J = 6.2 Hz, 2H), 6.70 (t, J = 2.3 Hz, 1H), 6.67 (t, J = 2.3 Hz, 1H), 5.09 (s, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 185.3, 136.1, 129.1, 129.0, 128.4, 127.4, 126.8, 123.7, 108.7, 54.0 ; IR ($\nu_{\max}$) 2941, 1592, 1468, 1425, 1204, 1155, 1066, 754; HRMS Calcd for $C_{12}H_{11}NO$ (M^+) 185.0841, Found 185.0826.



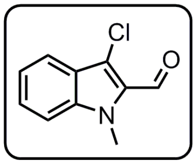
1-Benzyl-2-chloropyrrole-5-carbaldehyde 41. To a solution of *N*-benzyl-2-chloro-pyrrole (350 µL, 2 mmol) in DMF (465 µL, 6 mmol, 3 equiv.) at 0 °C under argon is added POCl$_3$ (550 µL, 6 mmol, 3 equiv.) dropwise. The mixture is stirred 20 min at r.t., 2 h under reflux (100 °C), cooled down to r.t., then immerged in an crushed ice/water bath. The resulting solution is neutralized by addition of powdered NaOAc, and the crude product is extracted with CH$_2$Cl$_2$, dried with MgSO$_4$, concentrated under reduced pressure, and purified by silica gel chromatography to afford 185 mg of **41** as a clear oil in 85% yield. Exhibited identical spectral data according to previous report.[i] R$_f$ 0.7 (petroleum ether/ethyl acetate 80/20); ^{1}H NMR (400 MHz, CDCl$_3$) δ 9.43 (s, 1H), 7.32-7.22 (m, 3H), 7.13 (br d, J = 7.3 Hz, 2H), 6.95 (d, J = 4.2 Hz, 1H), 6.28 (d, J = 4.2 Hz, 1H), 5.67 (s, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 178.4, 136.7, 130.9, 128.7, 128.6, 127.5, 126.9, 124.4, 109.4, 48.4; IR ($\nu_{\max}$) 3121, 2949, 1709, 1438, 1414, 1237, 1113, 1096 cm^{-1}; HRMS Calcd for $C_{12}H_{10}ClNO$ (M^+) 219.0451, Found 219.0433.



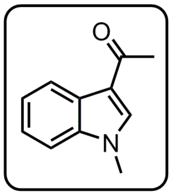
***N*-Methyl-2-(*p*-tolyl)indole 42.** Synthesized according to Conditions **A**. Clear oil; R_f 0.7 (petroleum ether/Et_2O 90/10); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (dt, $J = 7.8$ and 0.9 Hz, 1H), 7.40 (dd, $J = 8.1$ and 1.7 Hz, 2H), 7.36 (dd, $J = 7.4$ and 0.8 Hz, 1H), 7.28 (br d, $J = 8.1$ Hz, 2H), 7.22 (dd, $J = 7.0$ and 1.2 Hz, 1H), 7.13 (ddd, $J = 6.9$, 6.9, 1.0 Hz, 1H), 6.53 (d, $J = 0.7$ Hz, 1H), 3.74 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.6, 138.2, 137.8, 130.9, 129.3, 129.2, 127.9, 121.5, 120.3, 119.8, 109.5, 101.3, 31.1, 21.3; IR (ν_{max}) 2940, 1463, 1339, 1312, 1240, 1002, 751, 727 cm^{-1}; HRMS Calcd for $C_{16}H_{15}N$ (M^+) 221.1204, Found 221.1193.



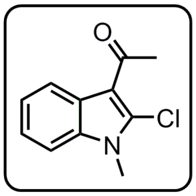
***N*-Methylindole-3-carbaldehyde 43**. To a solution of *N*-methylindole (130 µL, 1 mmol) in DMF (78 µL, 1 mmol, 1 eq) at 0 °C under argon is added $POCl_3$ (92 µL, 1 mmol, 1 eq) dropwise. The mixture is stirred 20 min at r.t., 1 h at 60 °C, cooled down to r.t., then immersed in an crushed ice/water bath. The resulting solution is neutralized by addition of powdered NaOAc, and the crude product is extracted with CH_2Cl_2, dried with $MgSO_4$, concentrated under reduced pressure, and purified by silica gel chromatography to afford 146 mg of **43** as a white solid in 92% yield; mp 69-70 °C; R_f 0.3 (petroleum ether/ethyl acetate 50/50); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.97 (s, 1H), 8.30 (dt, $J = 6.4$ and 1.2 Hz, 1H), 7.65 (s, 1H), 7.36-7.30 (m, 3H), 3.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.6, 139.2, 137.8, 125.2, 123.9, 122.9, 121.9, 118.0, 109.8, 33.6; IR (ν_{max}) 2934, 1592, 1453, 1282, 1204, 1154, 1059, 841, 719 cm^{-1}; HRMS Calcd for $C_{10}H_9NO$ (M^+) 159.0684, Found 159.0688.



3-Chloro-*N*-methylindole-2-carbaldehyde 44. To a solution of 3-Chloro-*N*-methylindole (140 μL, 1 mmol) in DMF (78 μL, 1 mmol, 1 equiv.) at 0 °C under argon is added $POCl_3$ (92 μL, 1 mmol, 1 equiv.) dropwise. The mixture is stirred 20 min at r.t., 2 h under reflux (100 °C), cooled down to r.t., then immersed in an crushed ice/water bath. The resulting solution is neutralized by addition of powdered NaOAc, and the crude product is extracted with CH_2Cl_2, dried with $MgSO_4$, concentrated under reduced pressure, and purified by silica gel chromatography to afford 86 mg of **44** as a white solid in 45% yield; mp 88-89 °C; R_f 0.7 (petroleum ether/ethyl acetate 50/50); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.12 (s, 1H), 8.30-8.28 (m, 1H), 7.35-7.30 (m, 3H), 3.81 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.9, 136.8, 136.0, 124.3, 124.0, 123.5, 121.3, 112.9, 109.4, 30.1; IR (ν_{max}) 1656, 1509, 1472, 1378, 1032, 798, 747 cm^{-1}; HRMS Calcd for $C_{10}H_8ClNO$ (M^+) 193.0294, Found 193.0298.



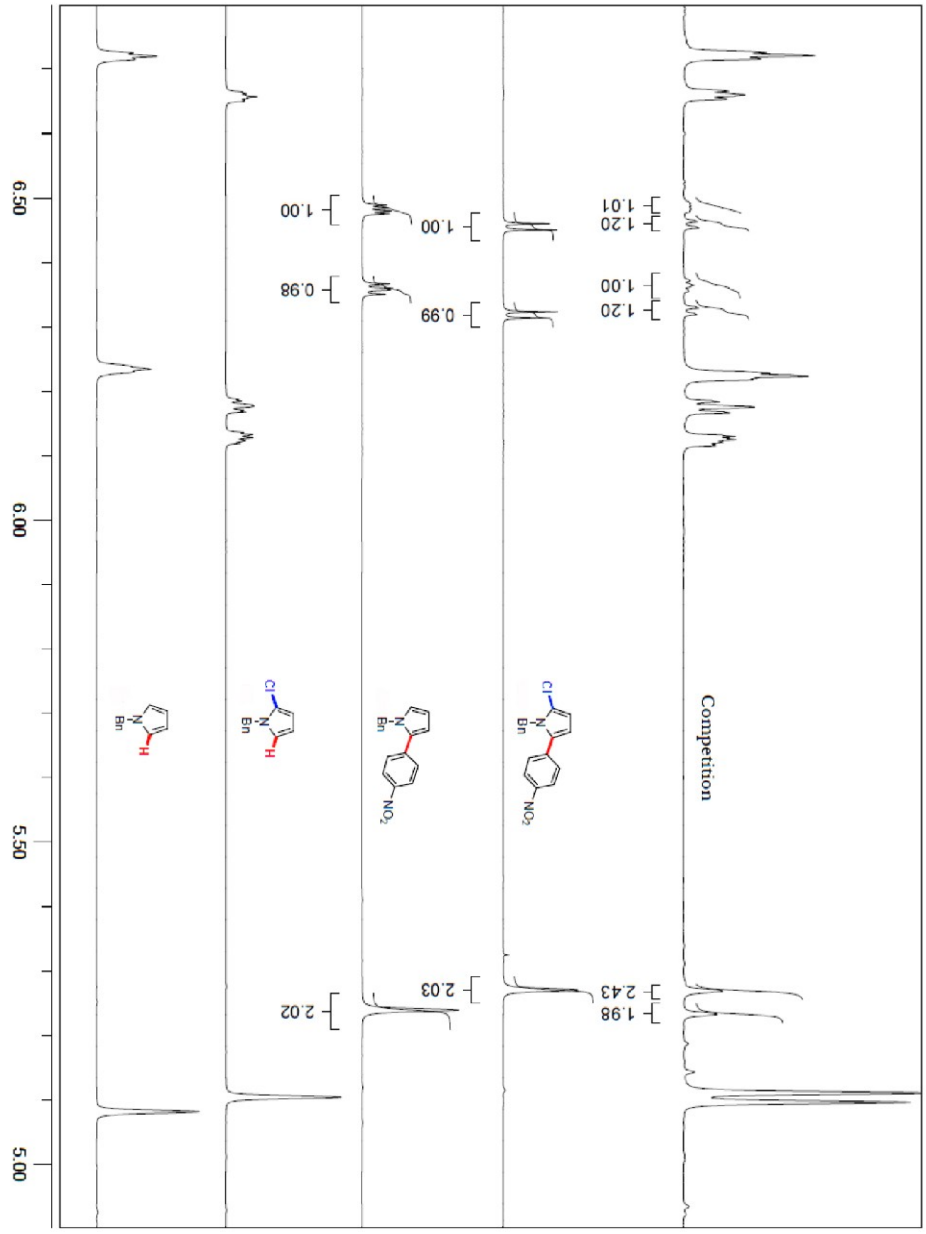
3-Acetyl-N-methylindole 45 (prepared by Dr. Benoit Liegault). To a solution of *N*-methylindole (250 μL, 2 mmol) in CH_2Cl_2 (10 mL) at 0 °C under argon are successively added acetyl chloride (213 µL, 3 mmol, 1.5 eq) and Et_2AlCl (1M in hexanes, 3 mL, 3 mmol, 1.5 eq) dropwise. The mixture is stirred 30 min at 0 °C then neutralized by addition of a saturated solution of $NaHCO_3$. The crude product is extracted with CH_2Cl_2, dried with MgSO4, concentrated under reduced pressure, and purified by silica gel chromatography to afford 230 mg of **45** as a white solid in 66% yield; R_f 0.4 (petroleum ether/ethyl acetate 50/50); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37(m, 1H), 7.68 (s, 1H), 7.35-7.27 (m, 3H), 3.82 (s, 3H), 2.51 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.9, 137.4, 135.7, 126.2, 123.3, 122.5, 116.9, 109.6, 3.47, 27.6; IR (ν_{max}) 3293, 3177, 1599, 1316, 1207, 1157, 1062 cm^{-1}; HRMS Calcd for $C_{11}H_{11}NO$ (M^+) 173.0841, Found 173.0834.



N-methyl-3-acetyl-2-chloroindole 46. $AlCl_3$ (0.08 g, 0.6 mmol, 2.0 eq) was weighed into a flask inside a glovebox. Dry DCM (1 mL) was added and the mixture cooled to 0 °C with stirring. Acetic anhydride (0.04 mL, 0.45 mmol, 1.5 eq) was added dropwise. N-methyl-2-chloroindole (0.05 g, 0.3 mmol, 1.0 eq) was dissolved in dry DCM (1 mL) in a separate flask, and added to the solution dropwise via a syringe. The reaction mixture was warmed up to room temperature and 0.3 mL of nitromethane was added as a co-solvent. The reaction was run overnight. Afterwards, the crude mixture was washed with water, the aqueous phase was extracted with DCM. The organic extracts were combined, dried over $MgSO_4$, concentrated under reduced pressure, and purified by silica gel chromatography to afford 0.03 g of **46** as a white solid in 52% yield. R_f 0.4 (petroleum ether/EtOAc 80/20); mp 99-100 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39-8.36 (m, 1H), 7.32-7.28 (m, 3H), 3.79 (s, 3H), 2.68

(s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.8, 135.6, 131.7, 125.8, 123.6, 123.0, 122.2, 113.3, 109.2, 30.8, 30.3; IR (ν_{max}) 2936, 1646, 1492, 1469, 1368, 1209, 935 cm^{-1}; HRMS Calcd for $C_{11}H_{10}ClNO$ (M^+) 207.0451, Found 207.0443.

7. APPENDIX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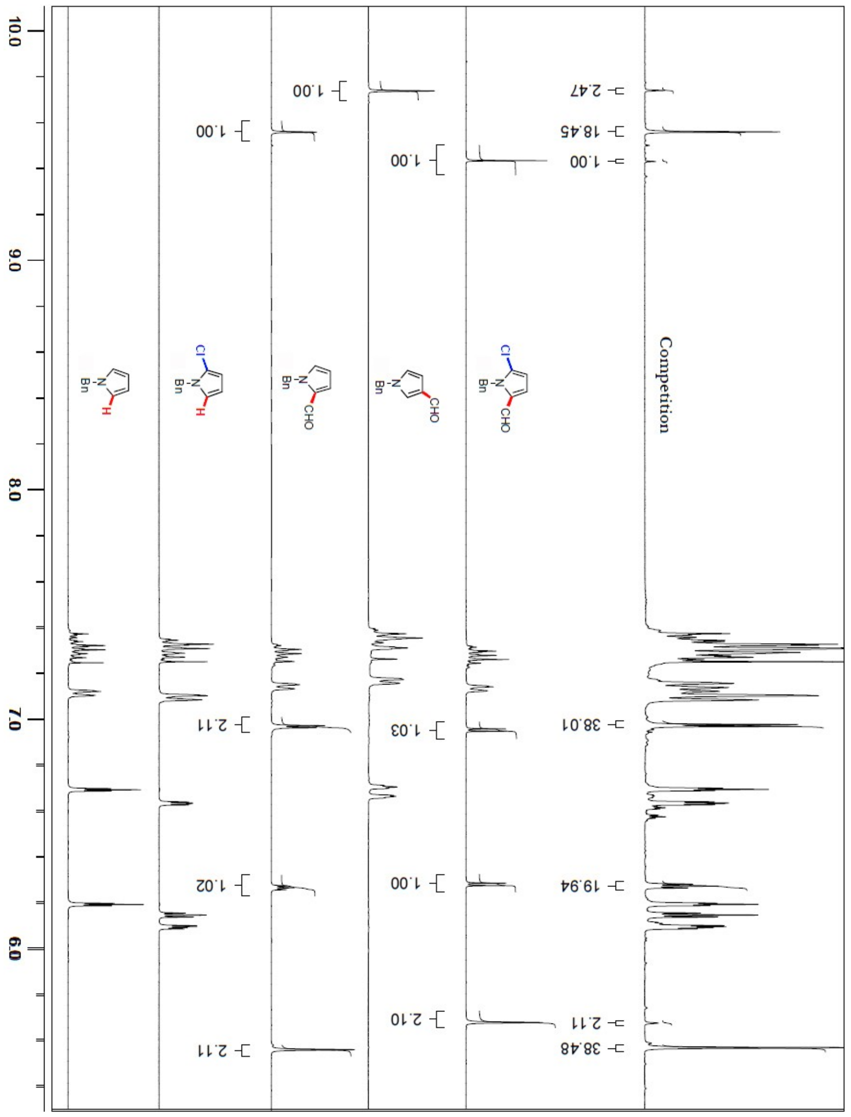
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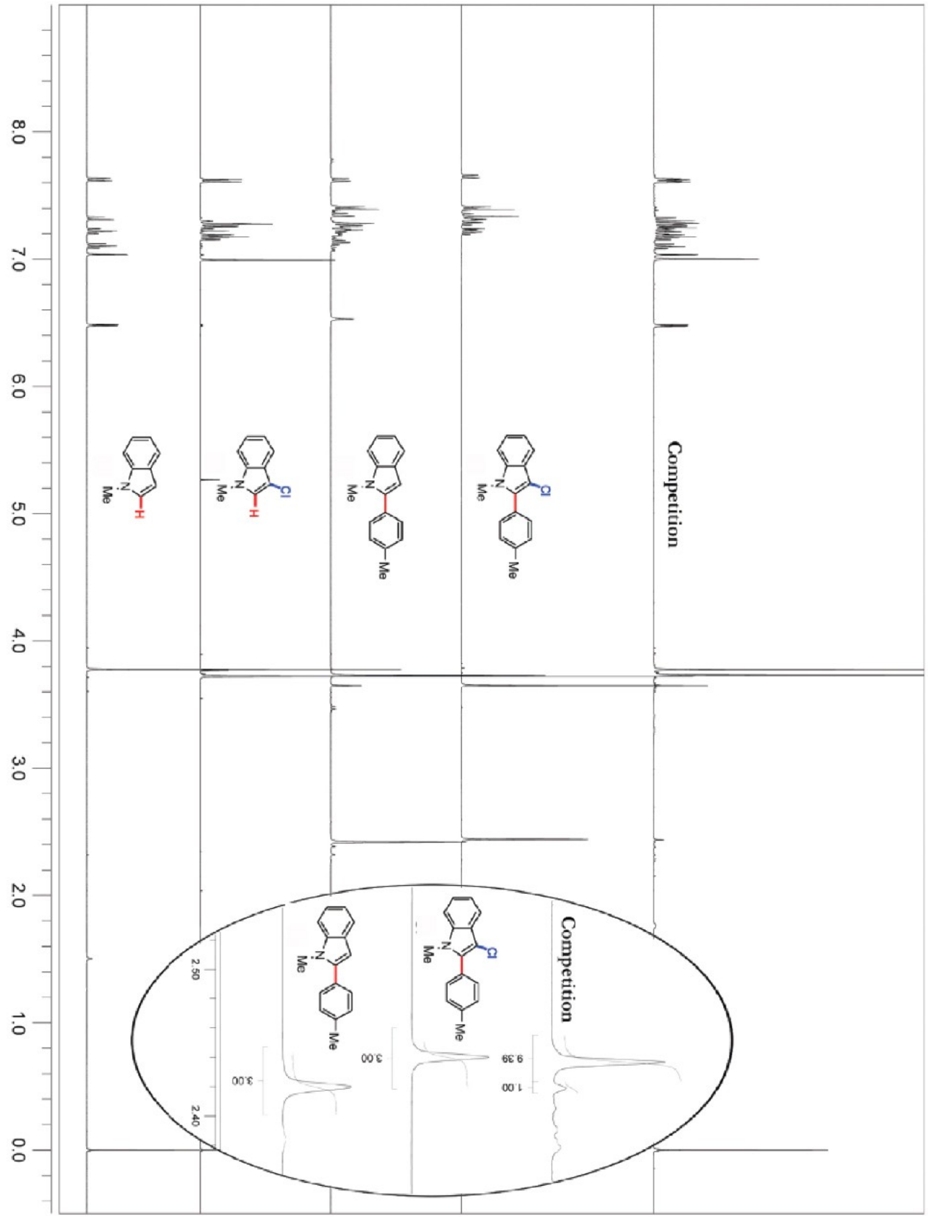
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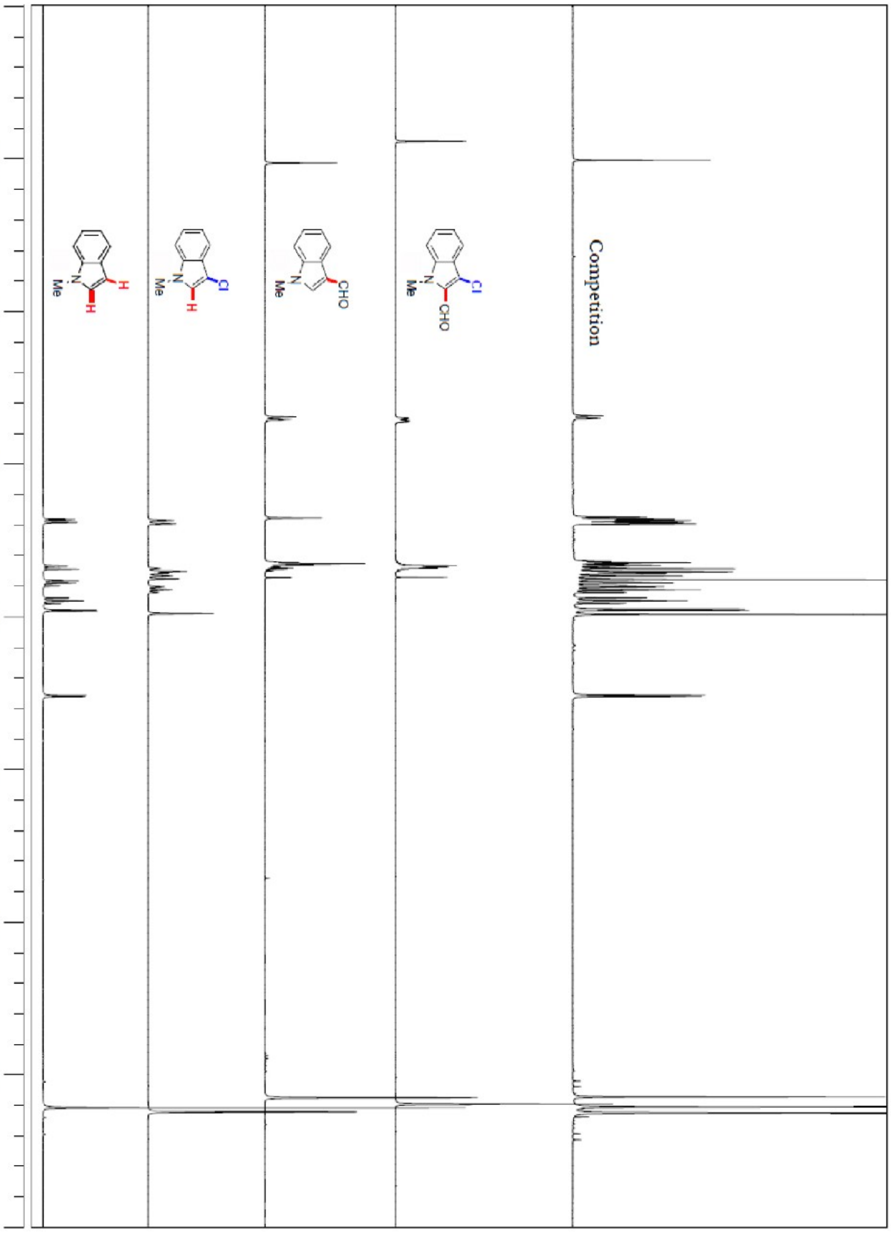
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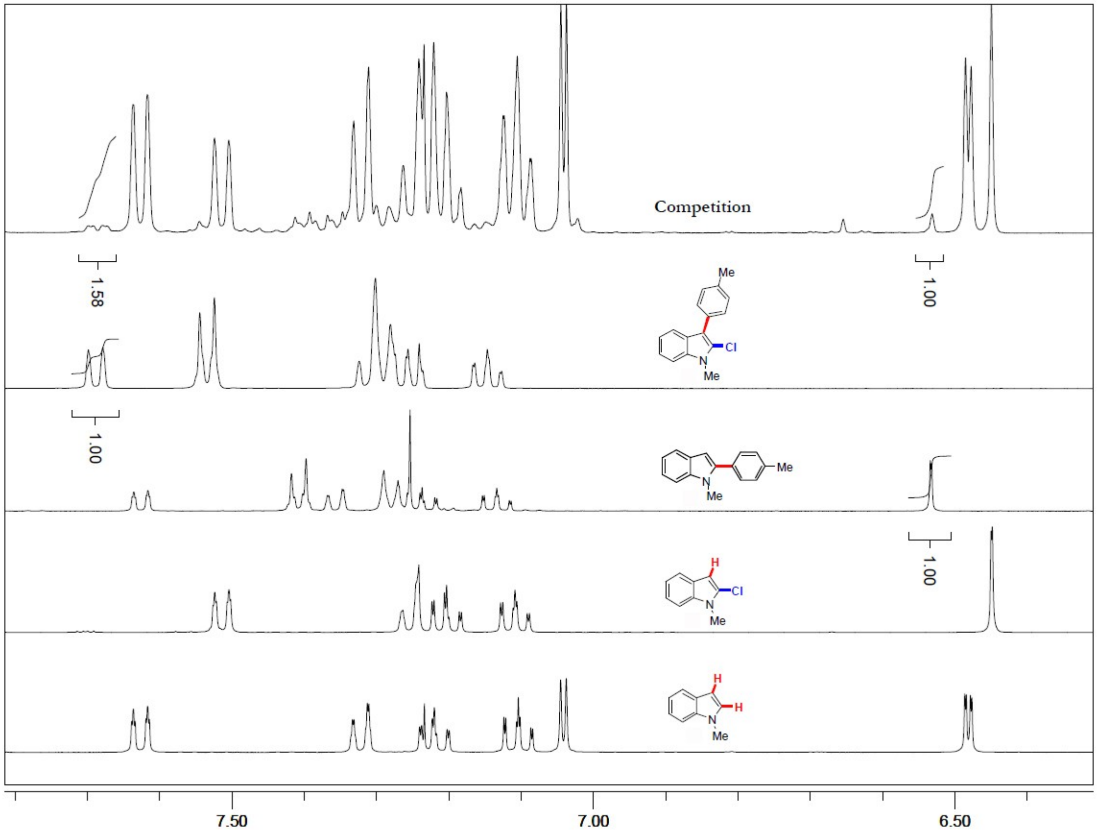
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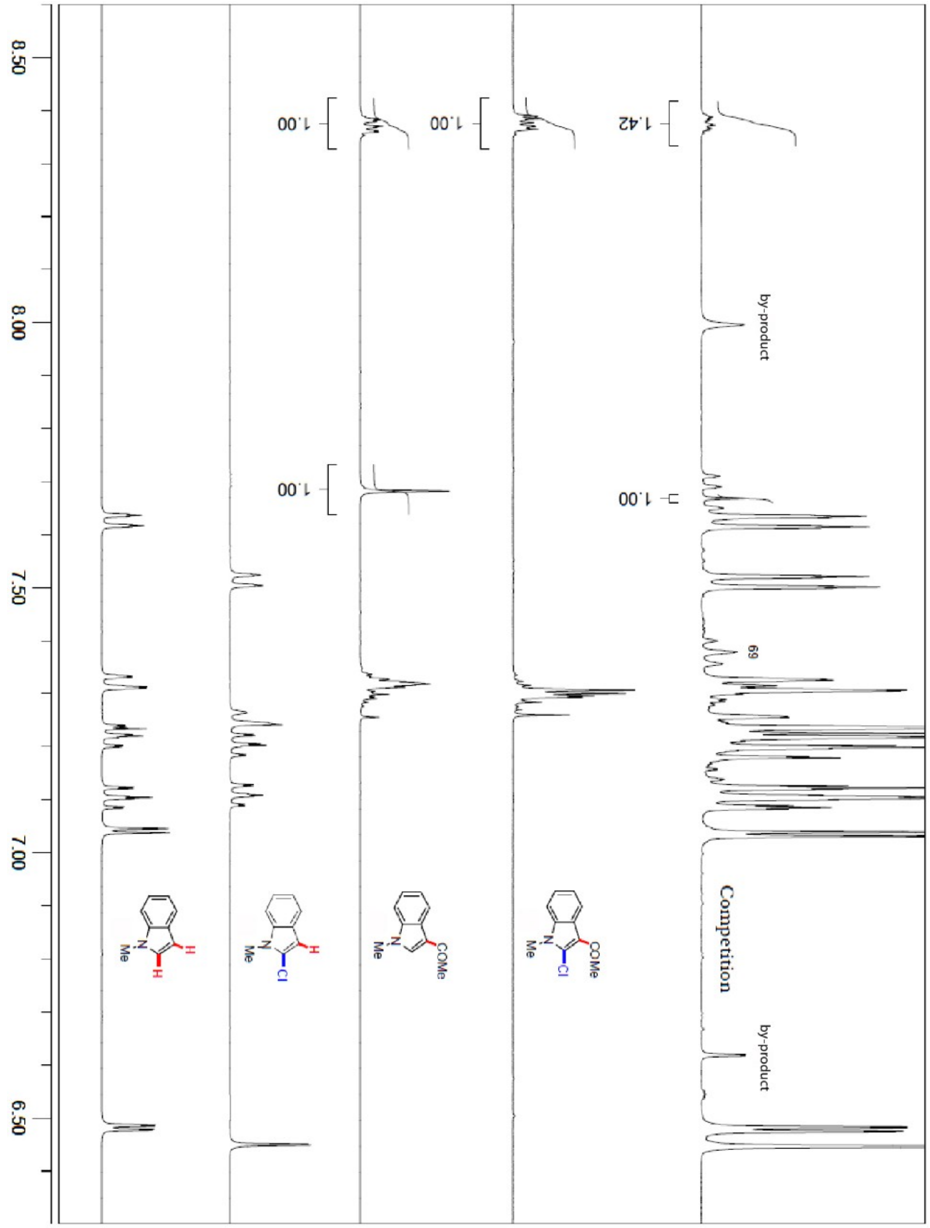
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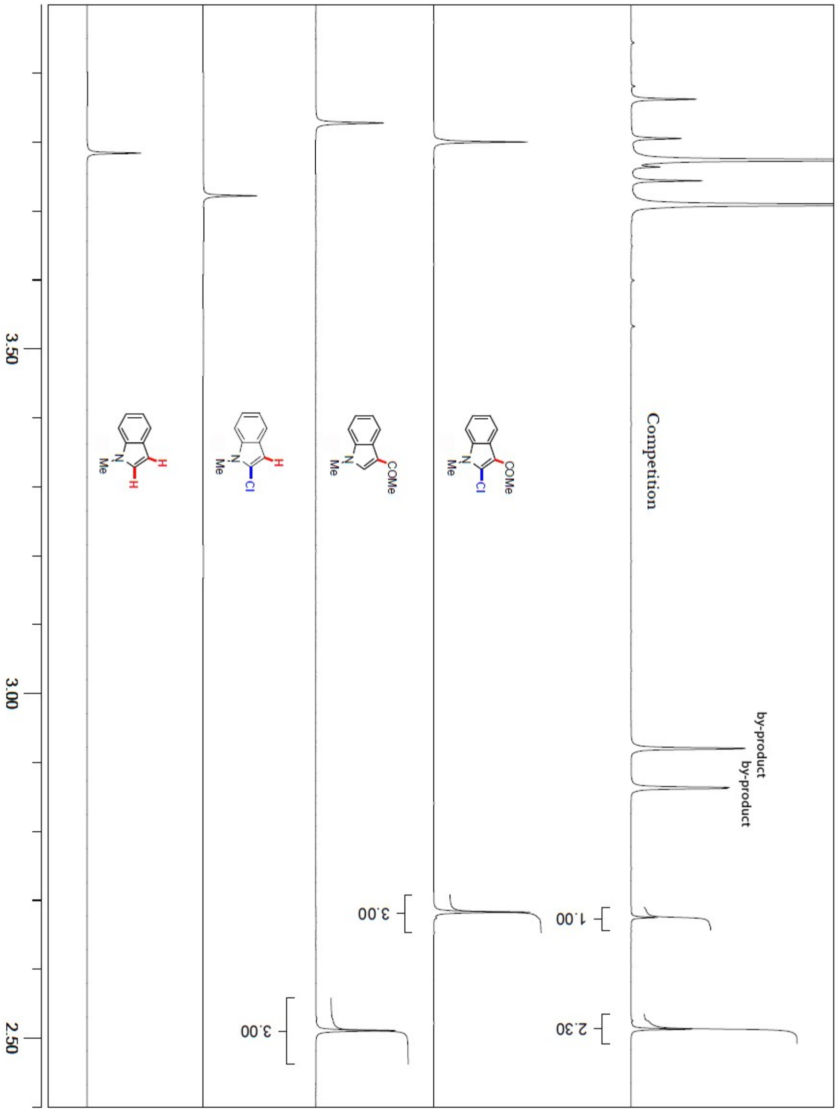
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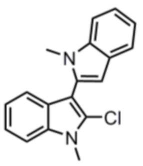
By-product: 
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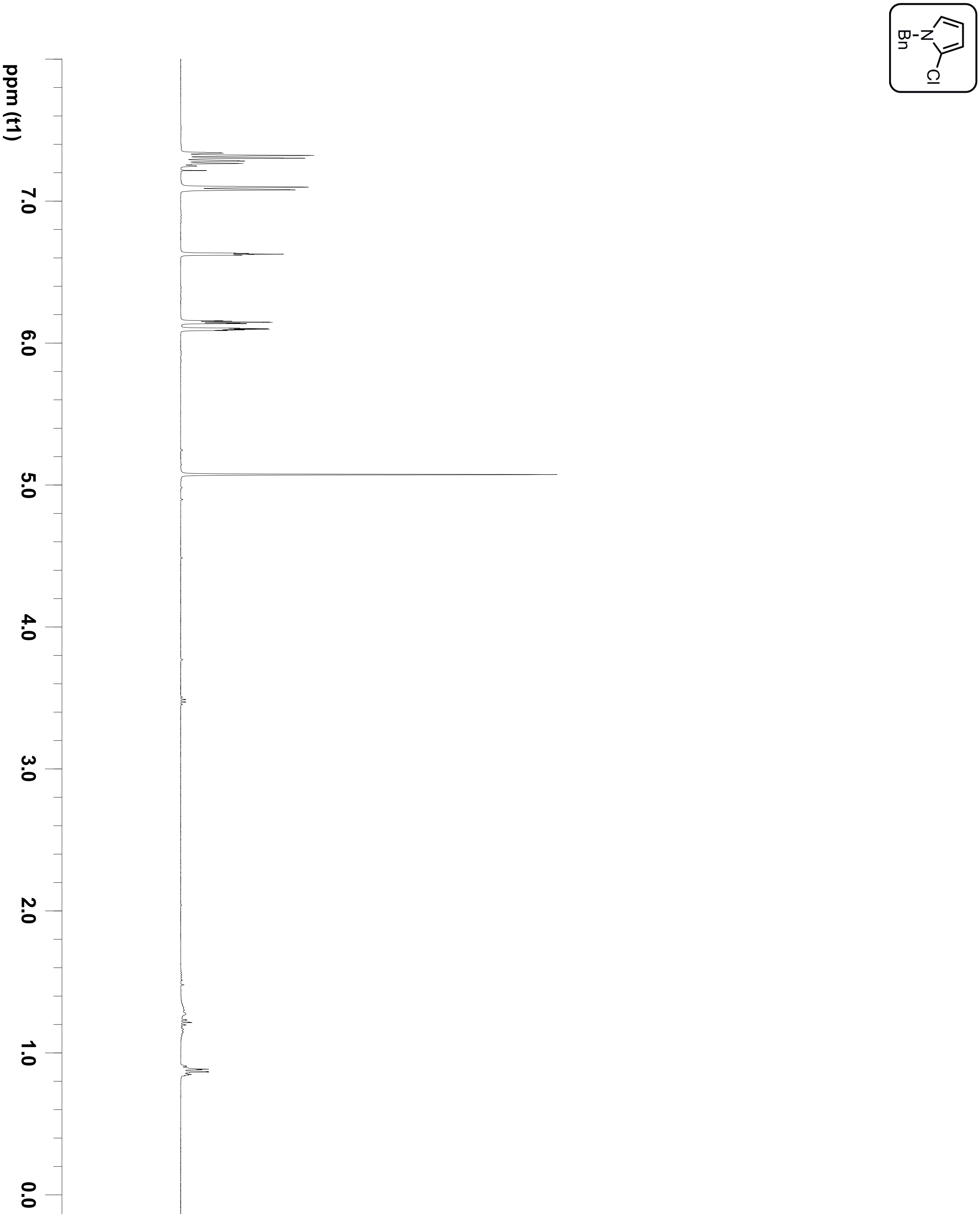
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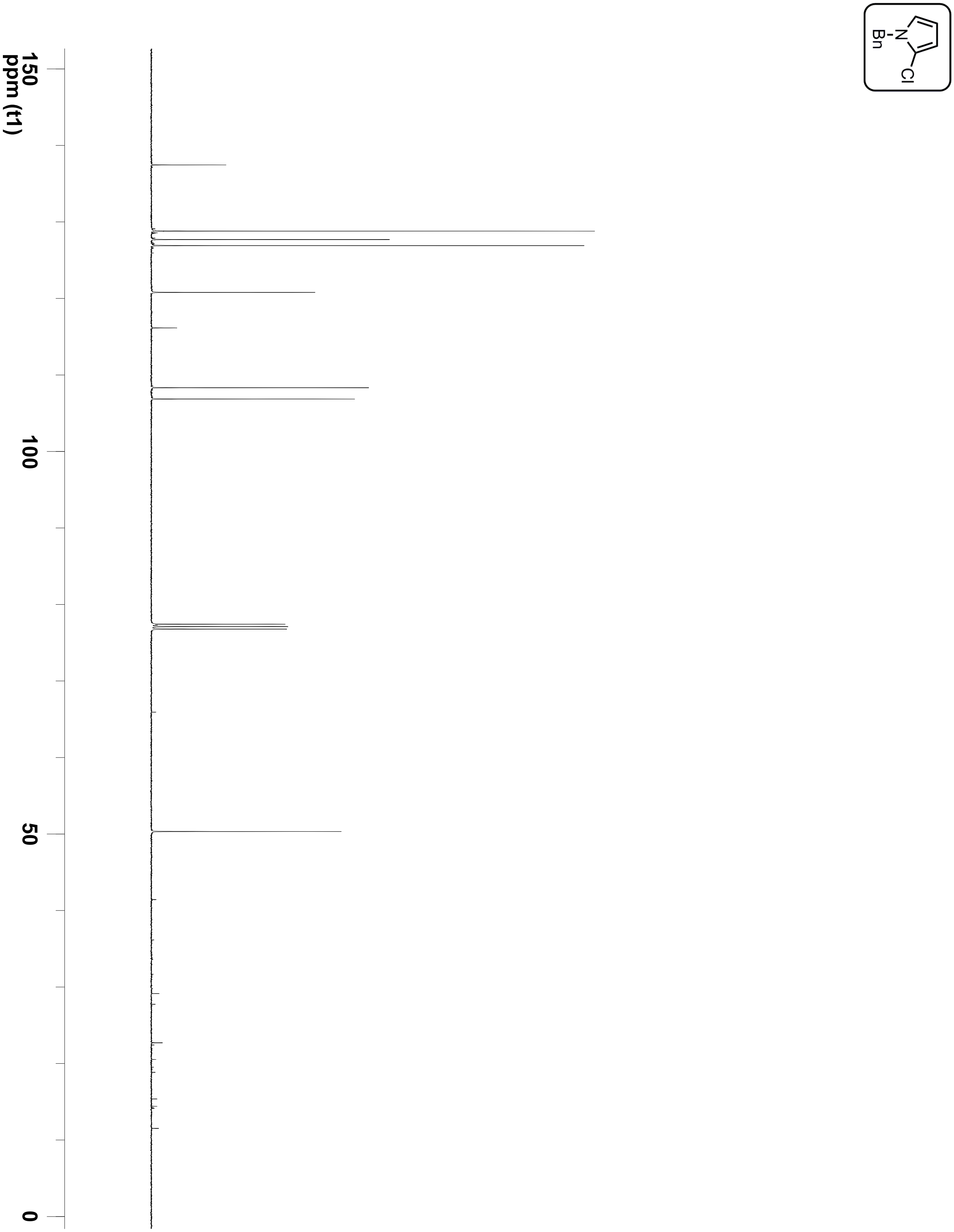

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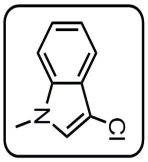
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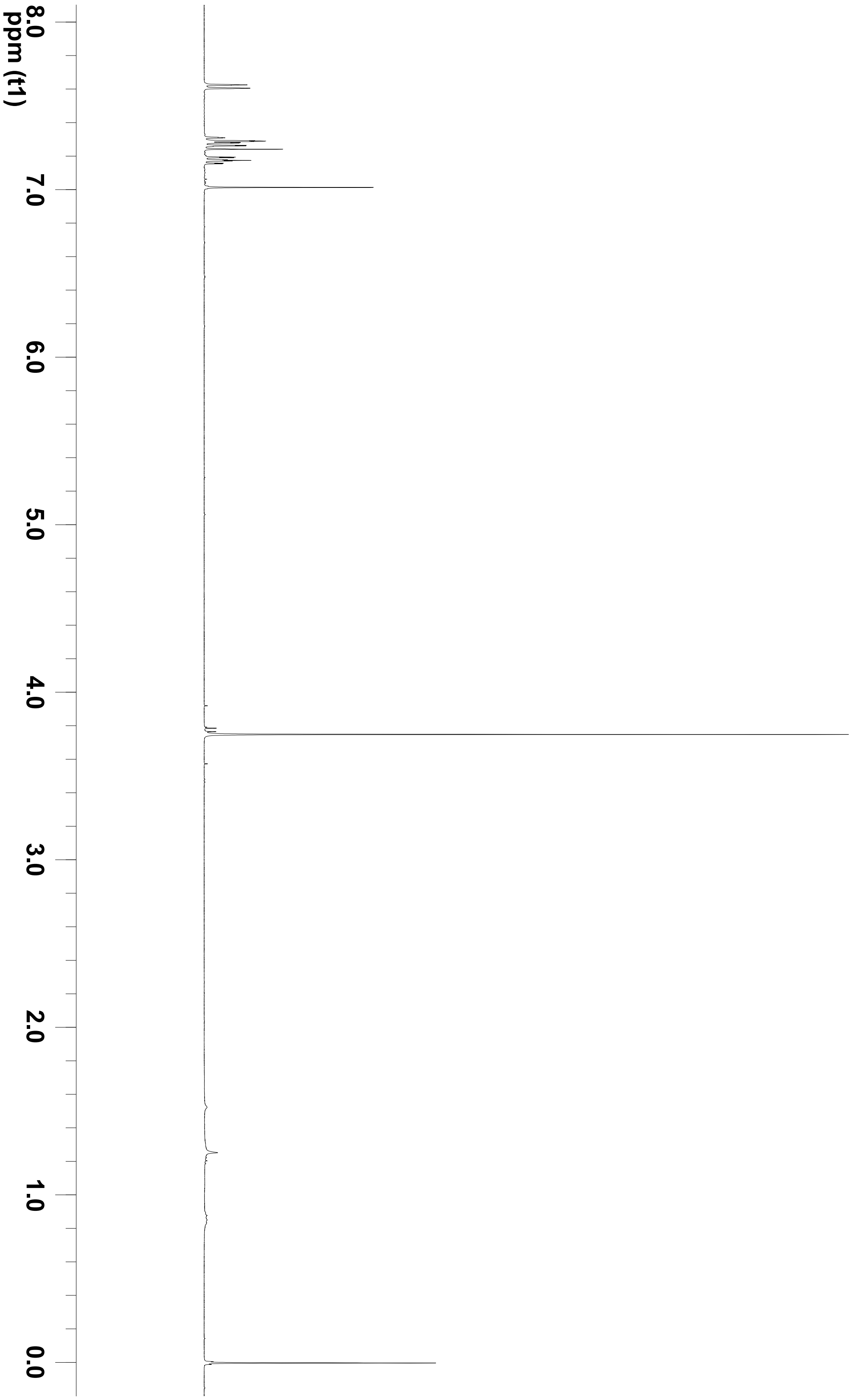
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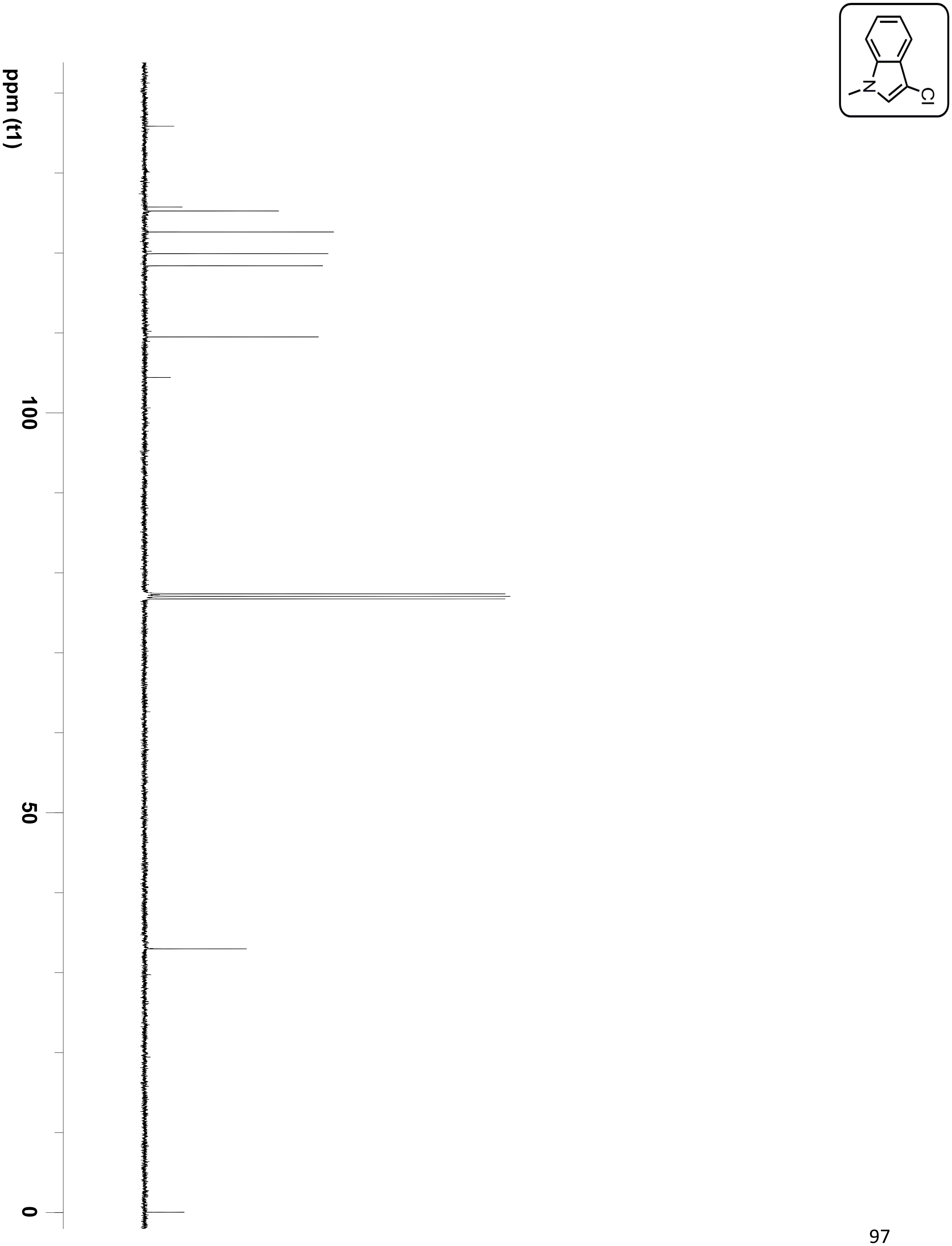
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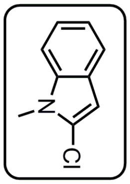
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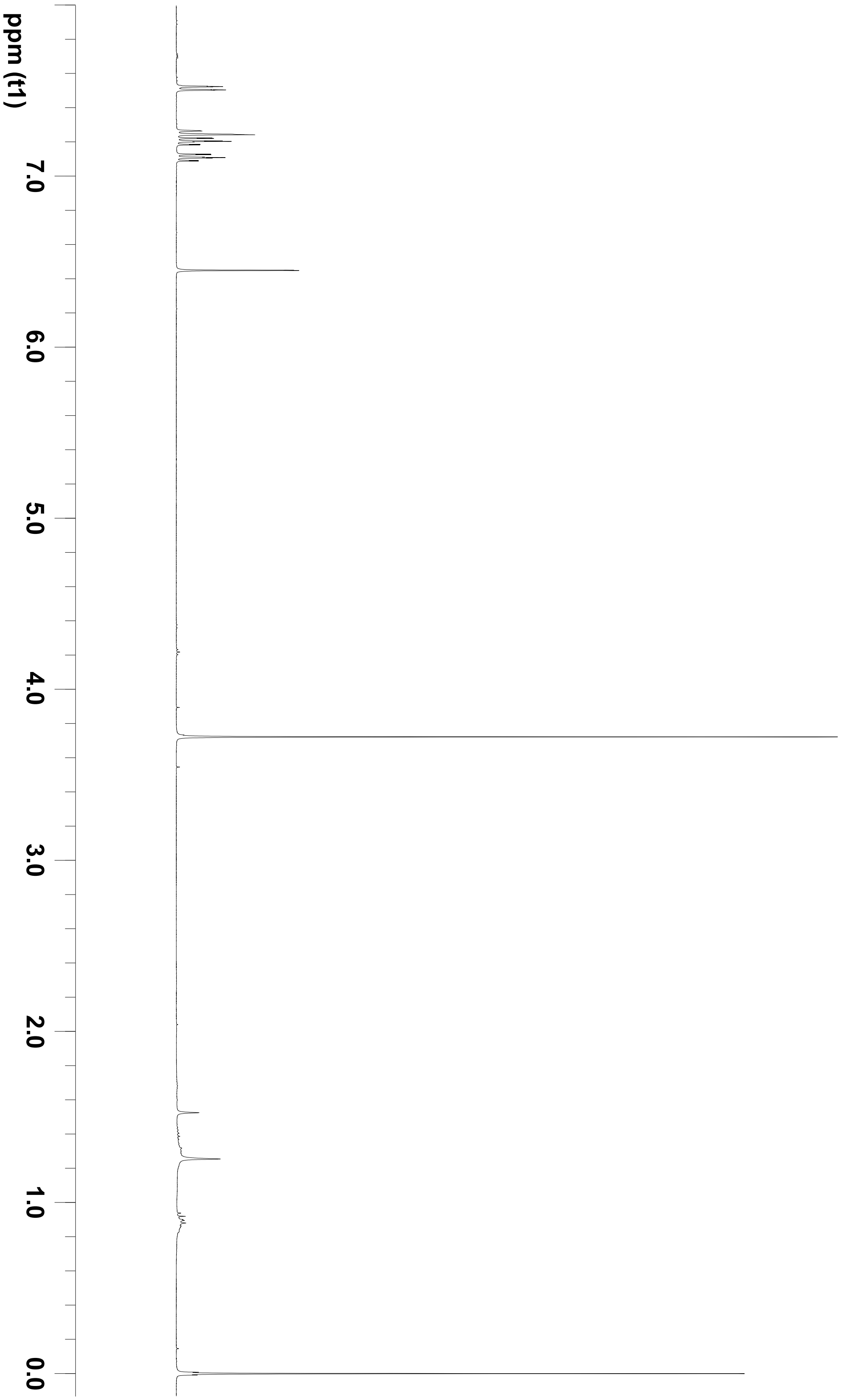
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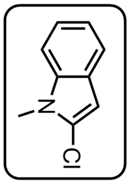
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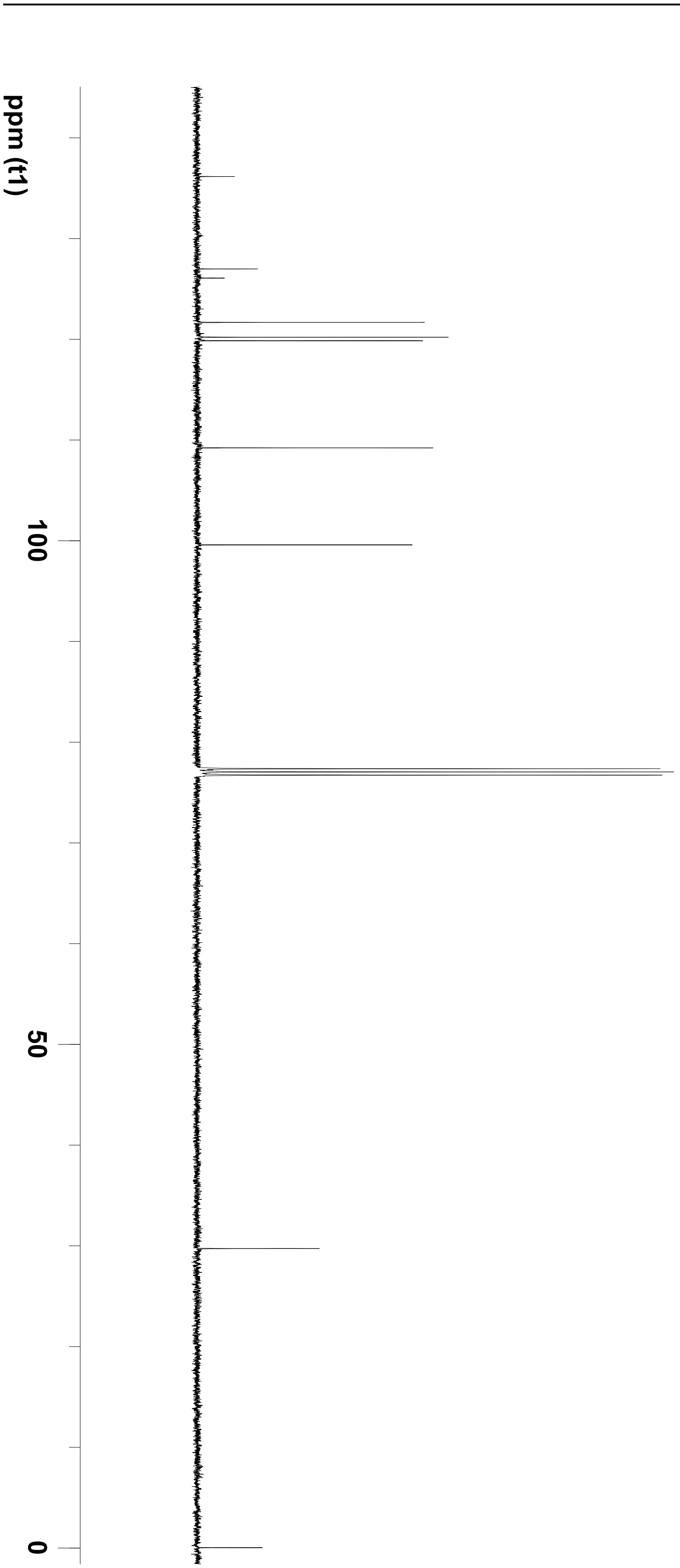
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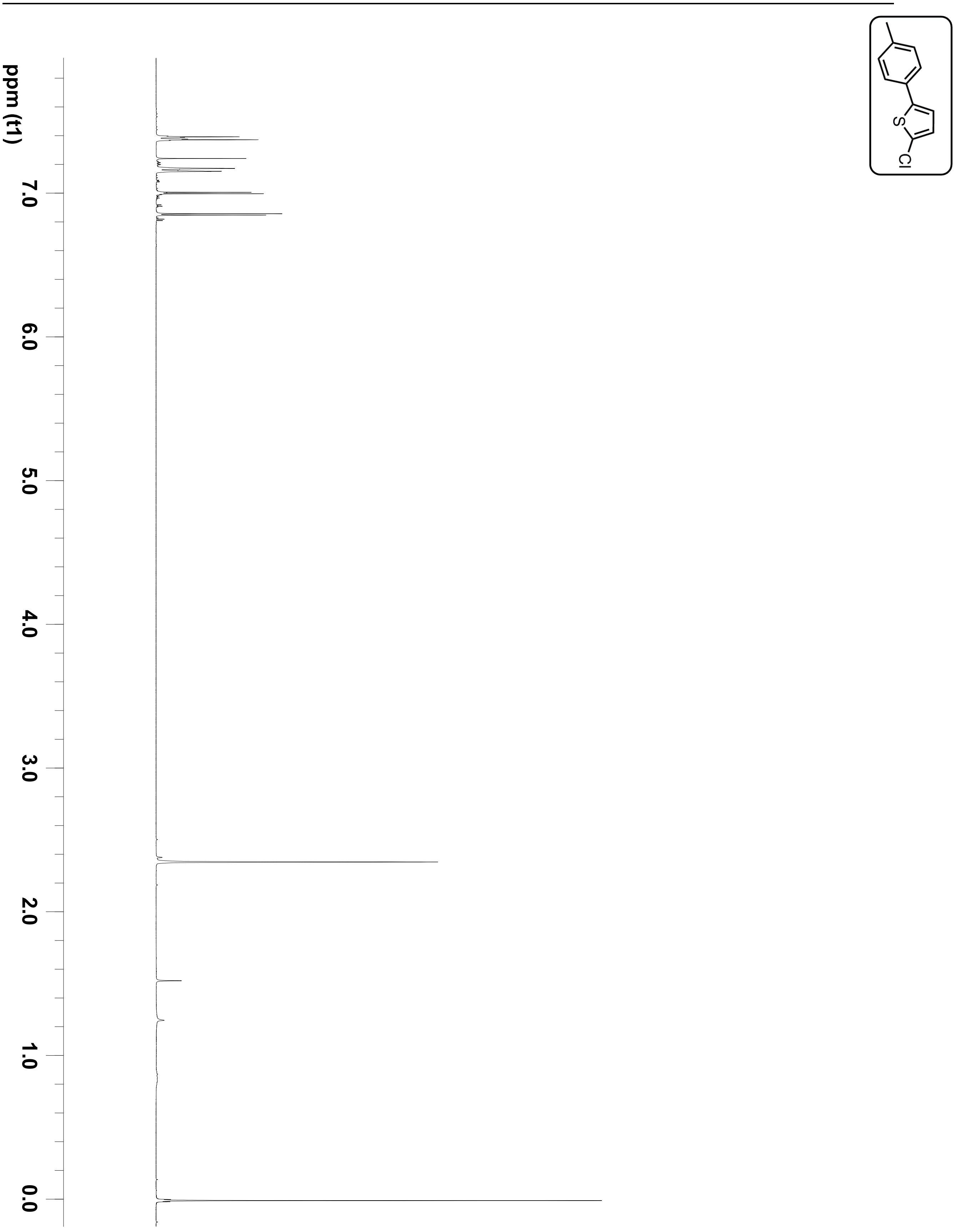
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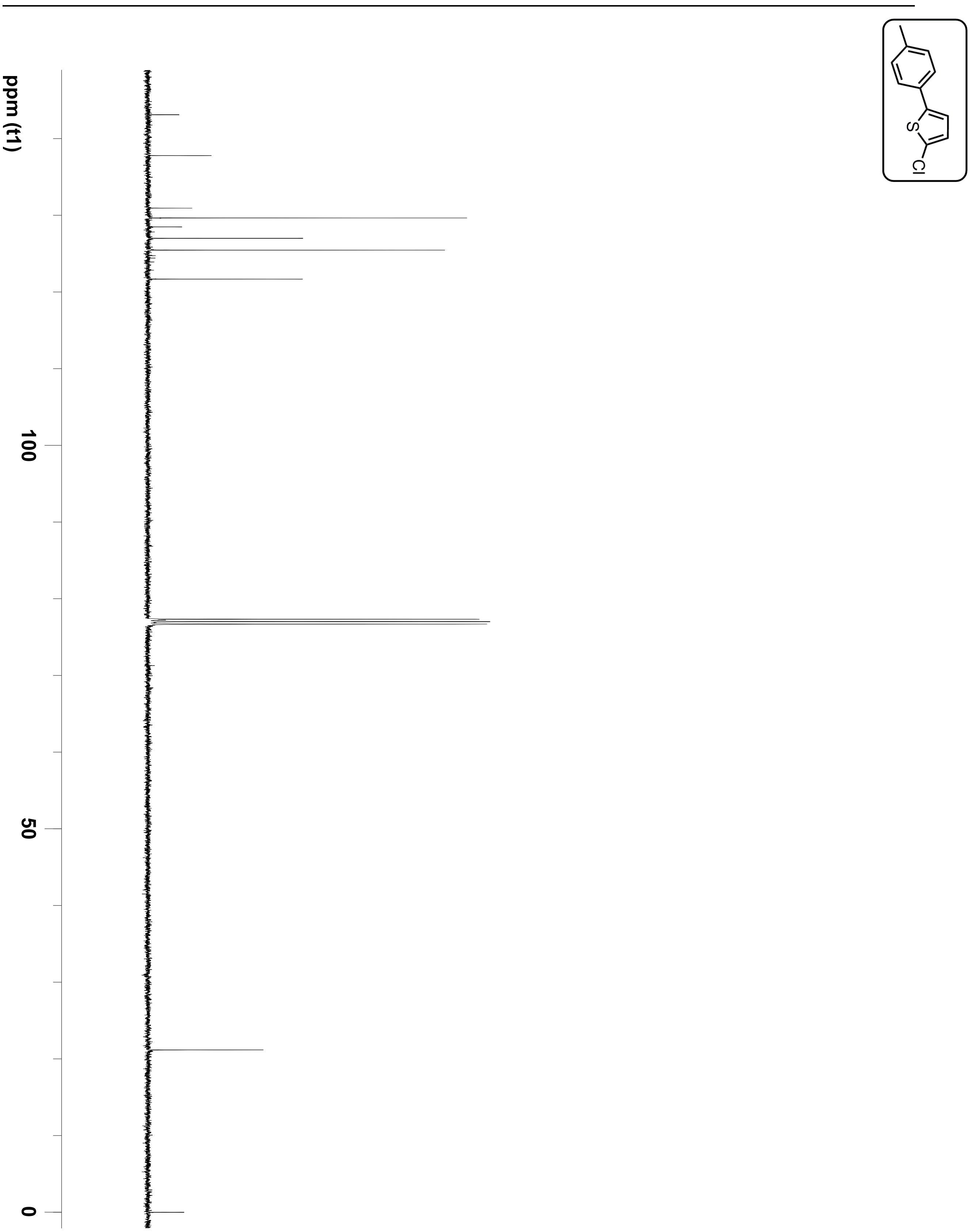
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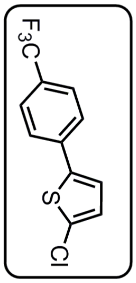
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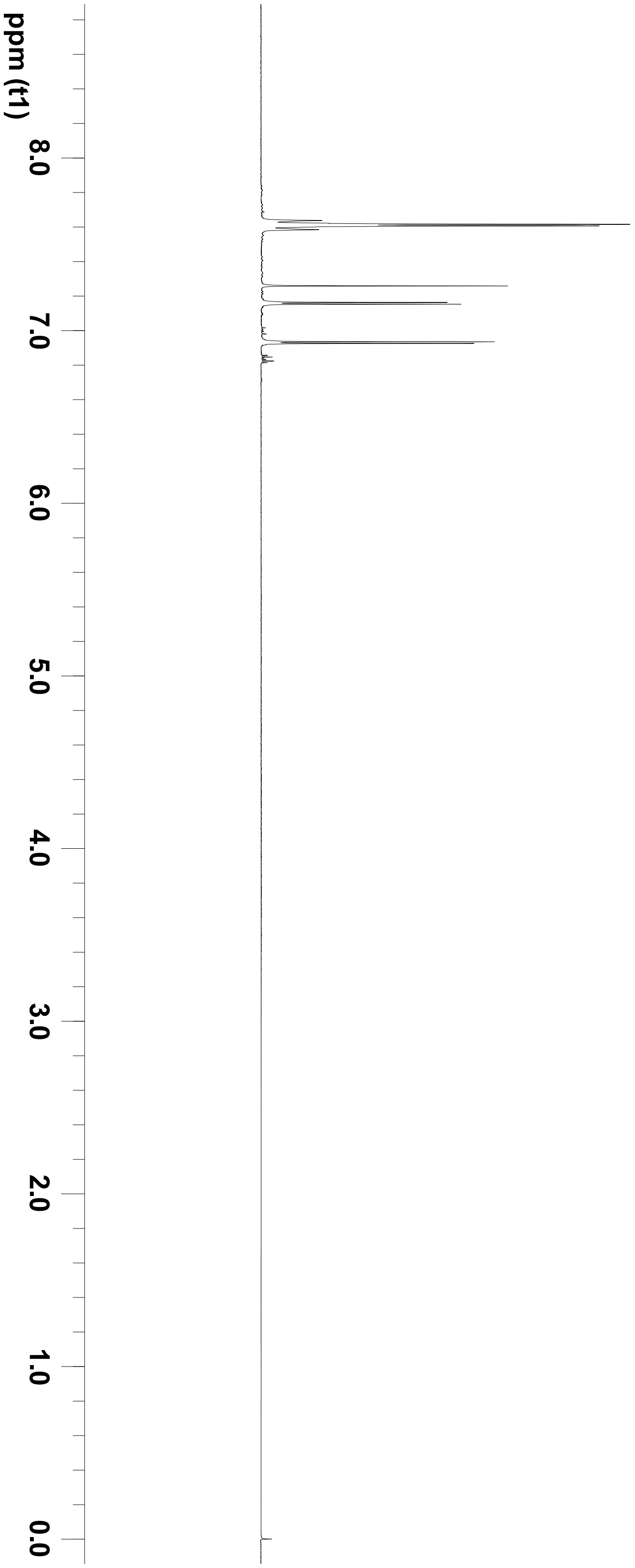
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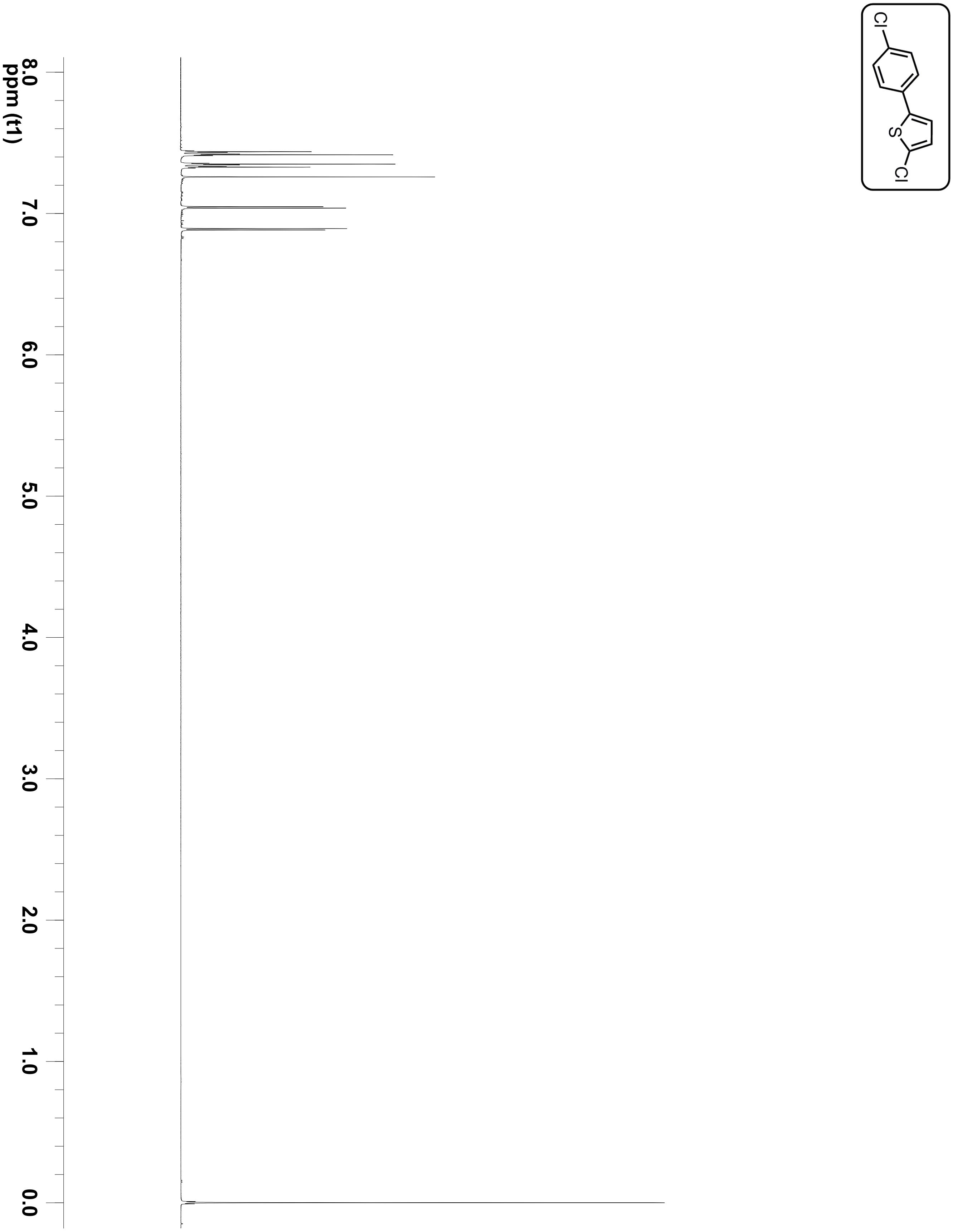

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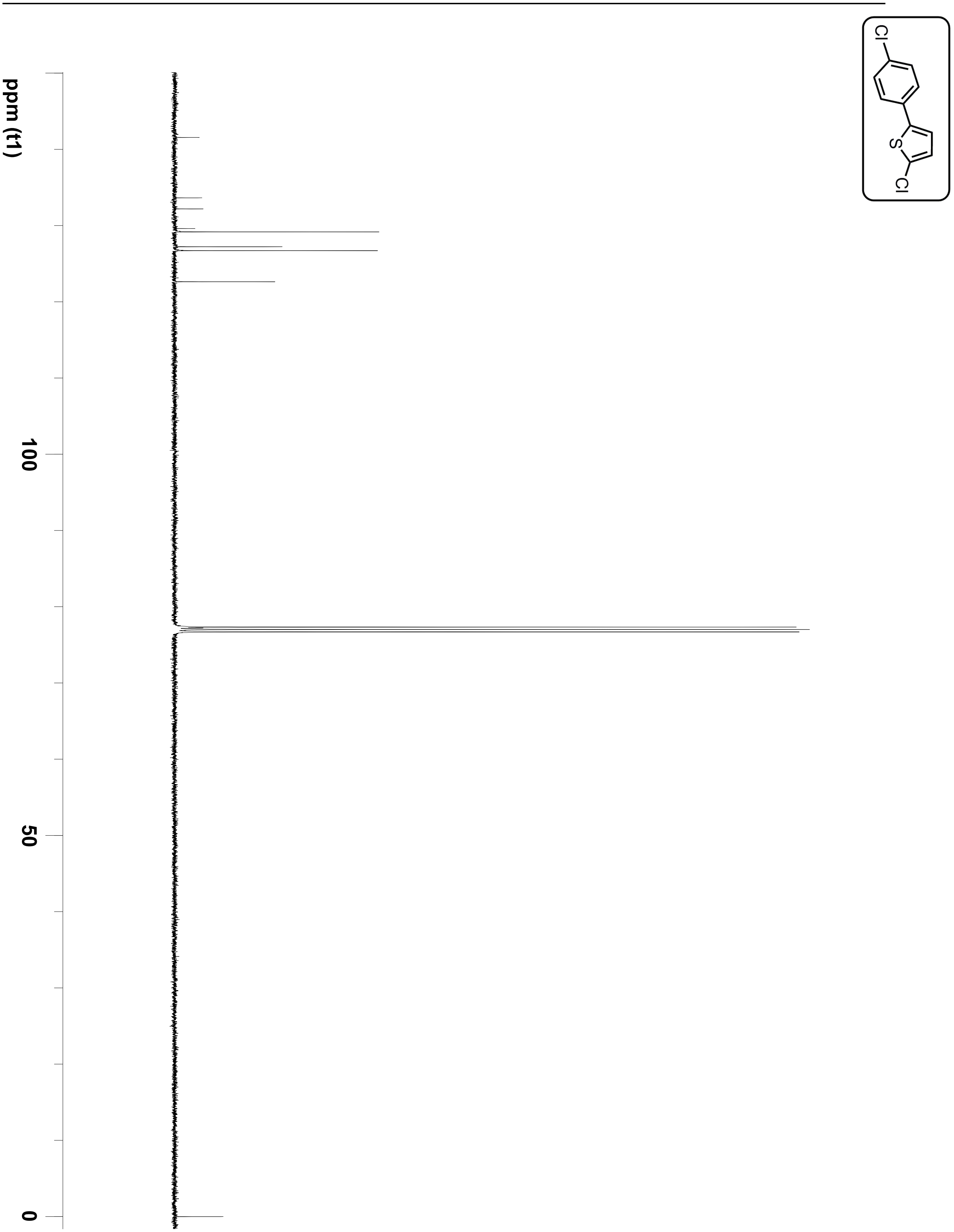
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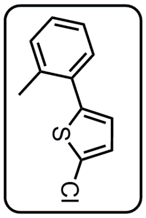
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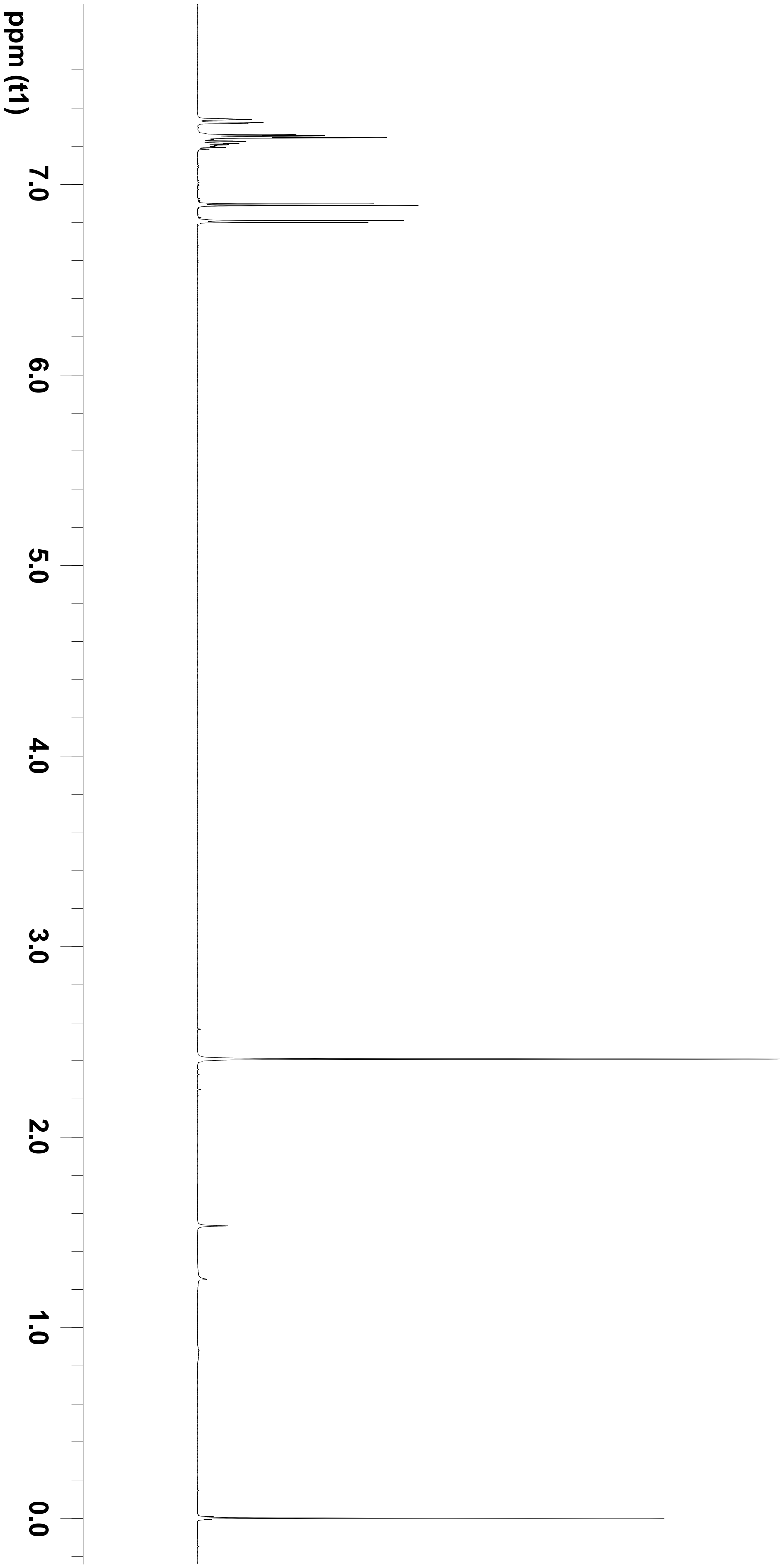
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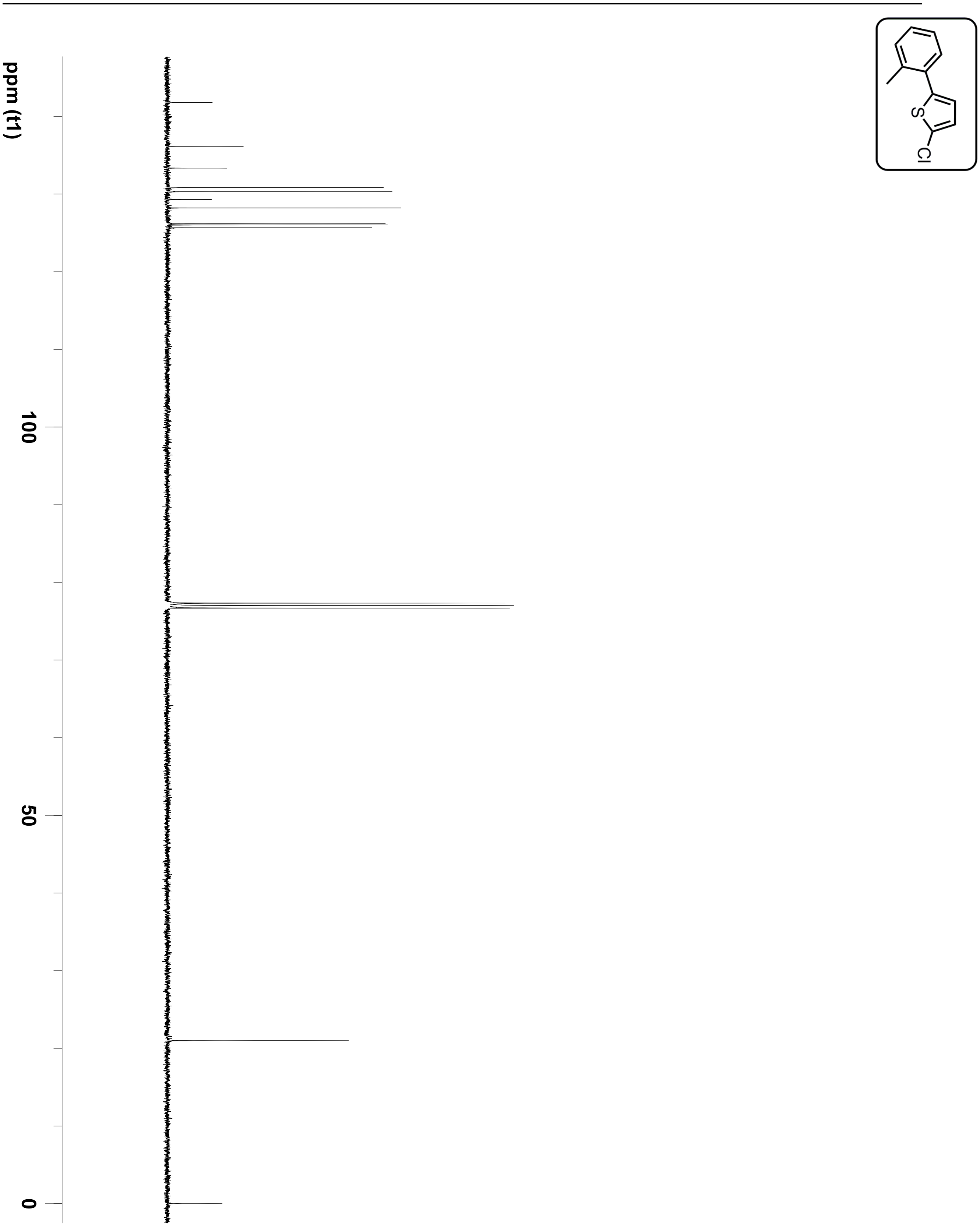
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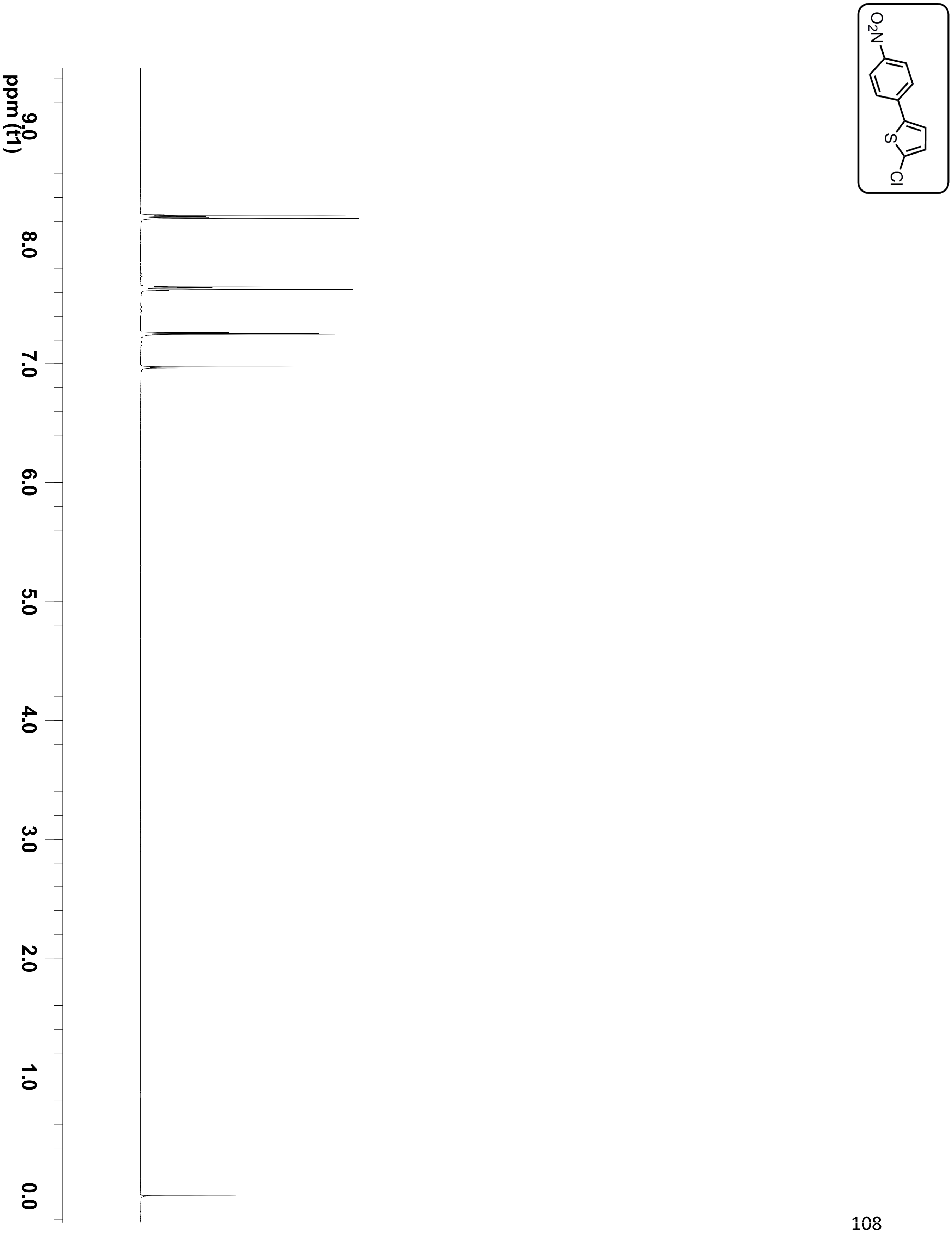
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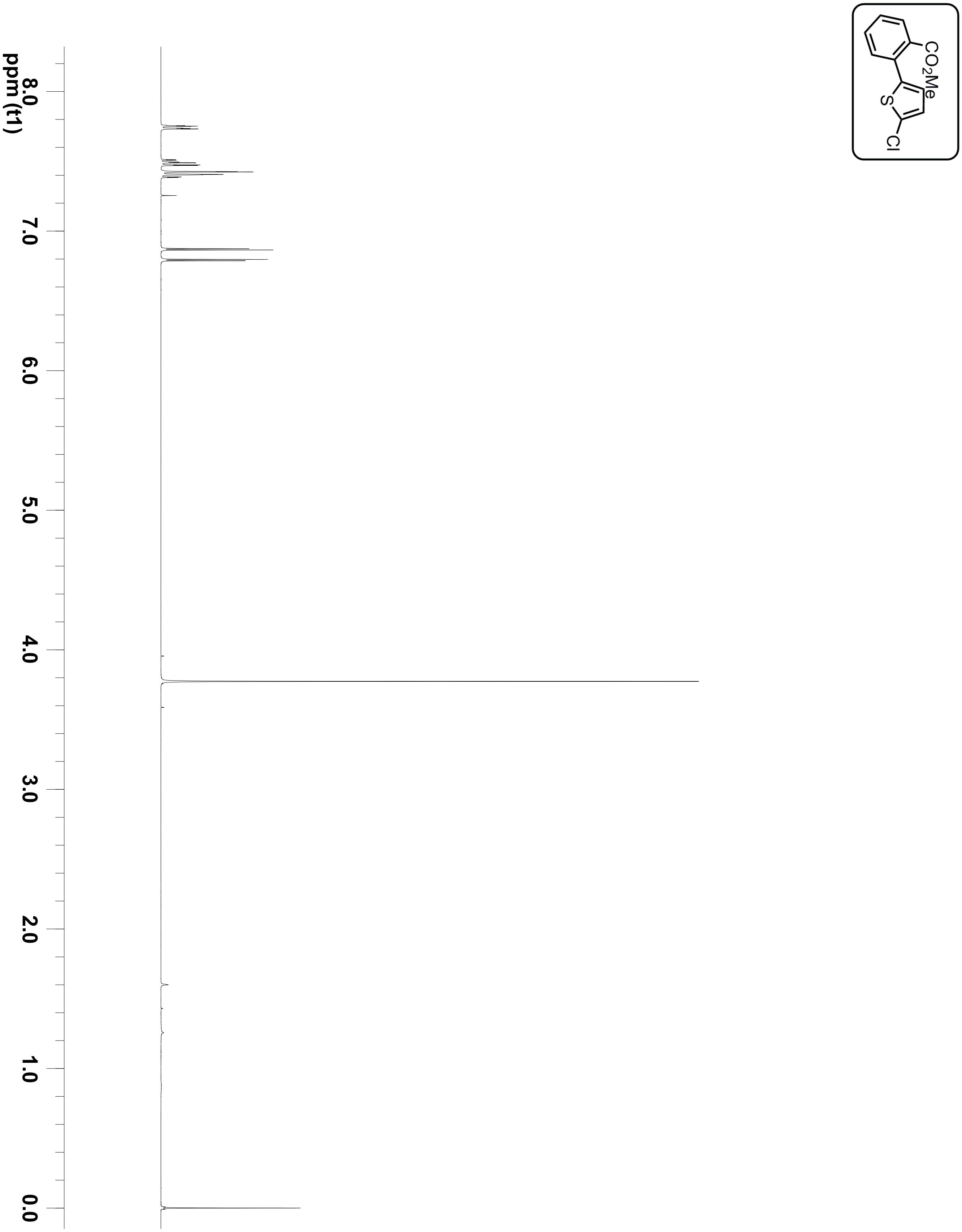
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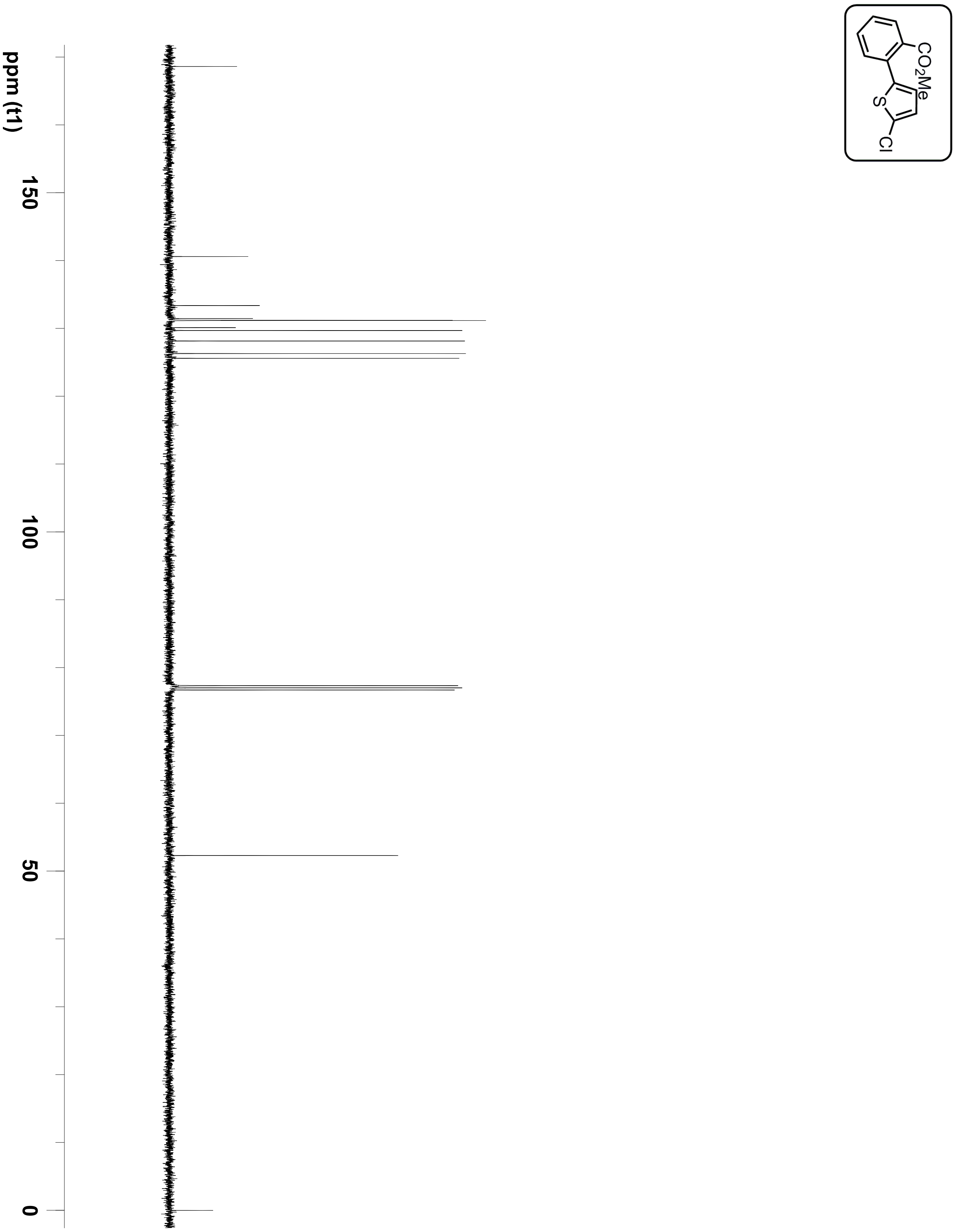
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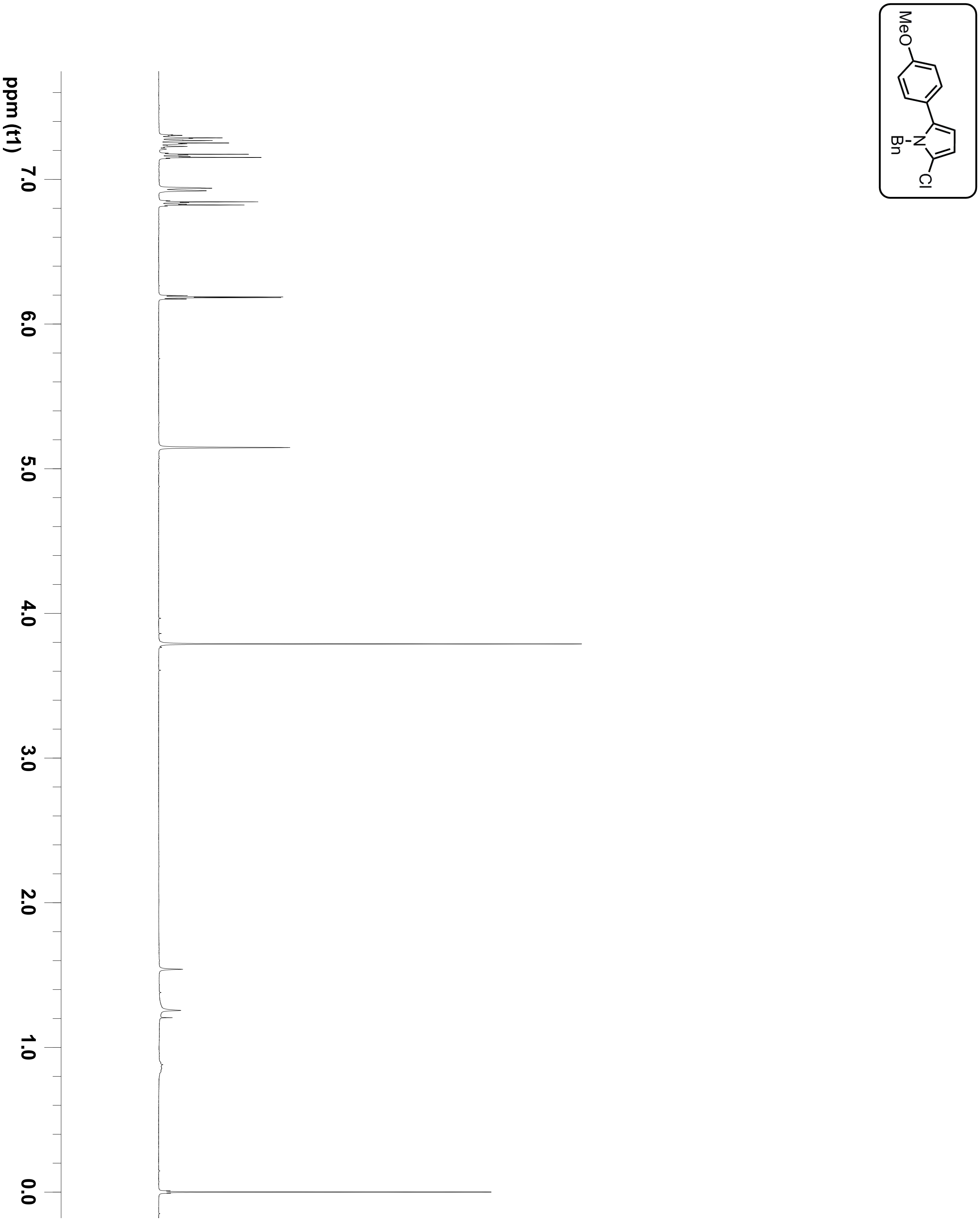
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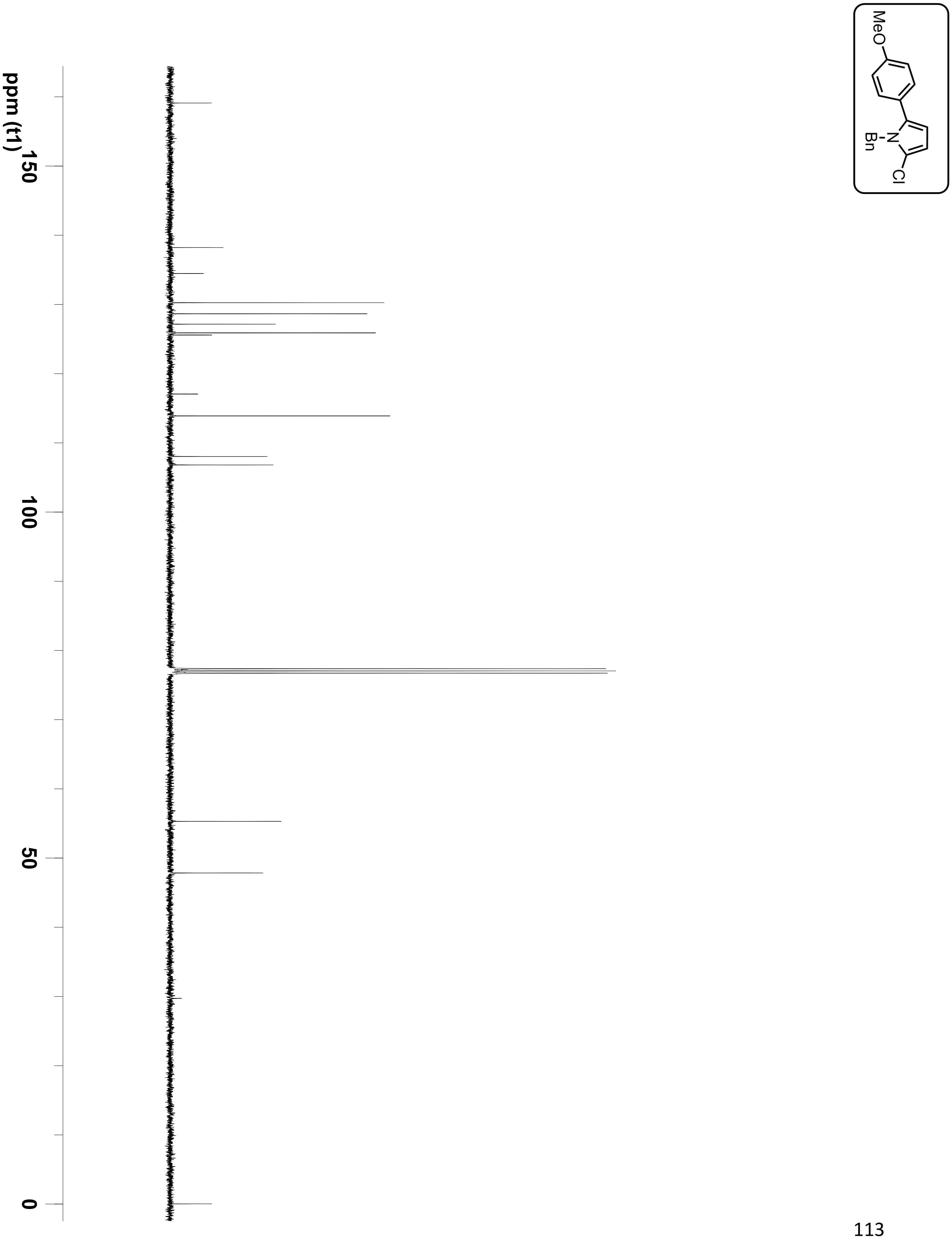
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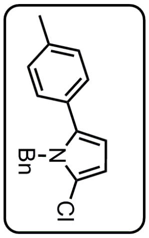
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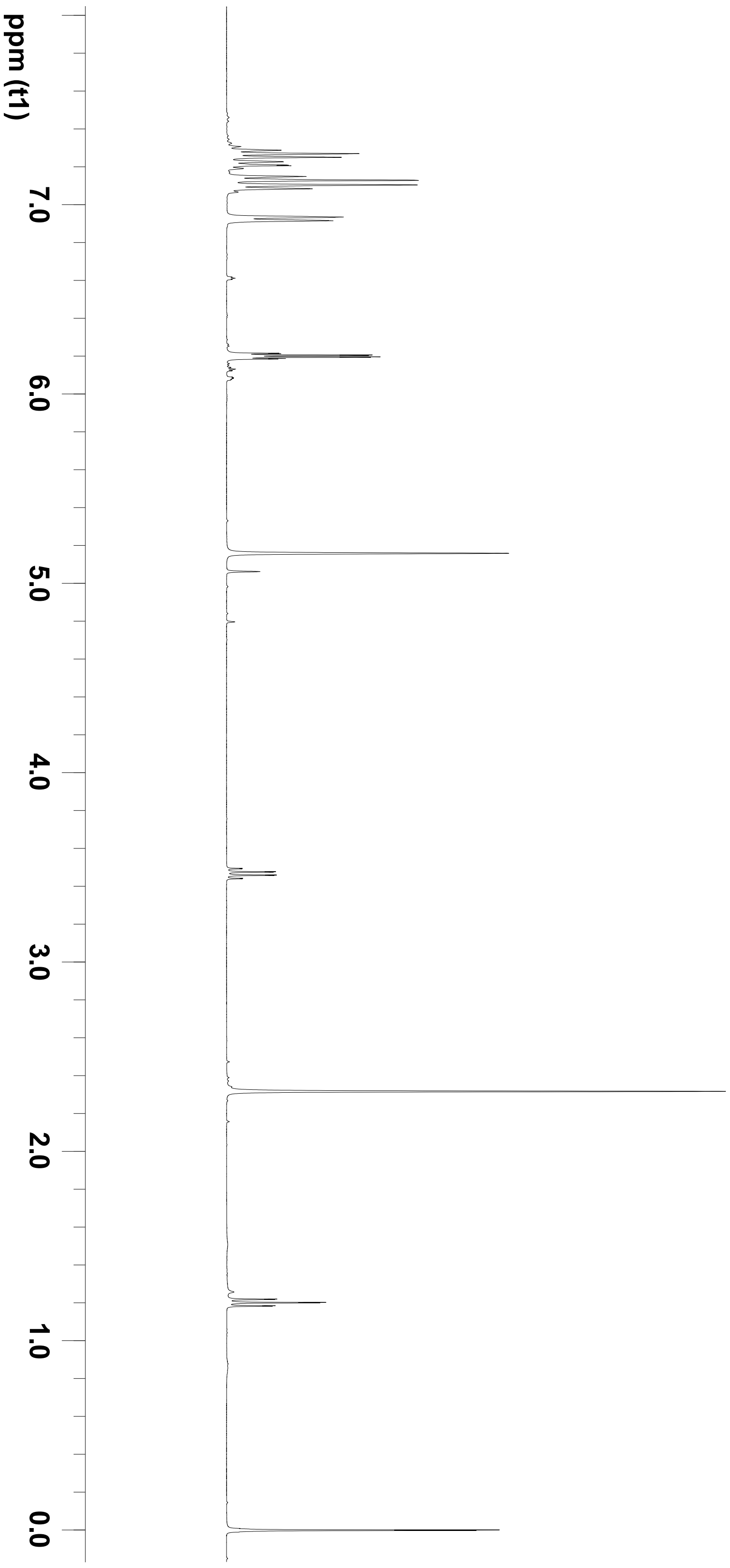
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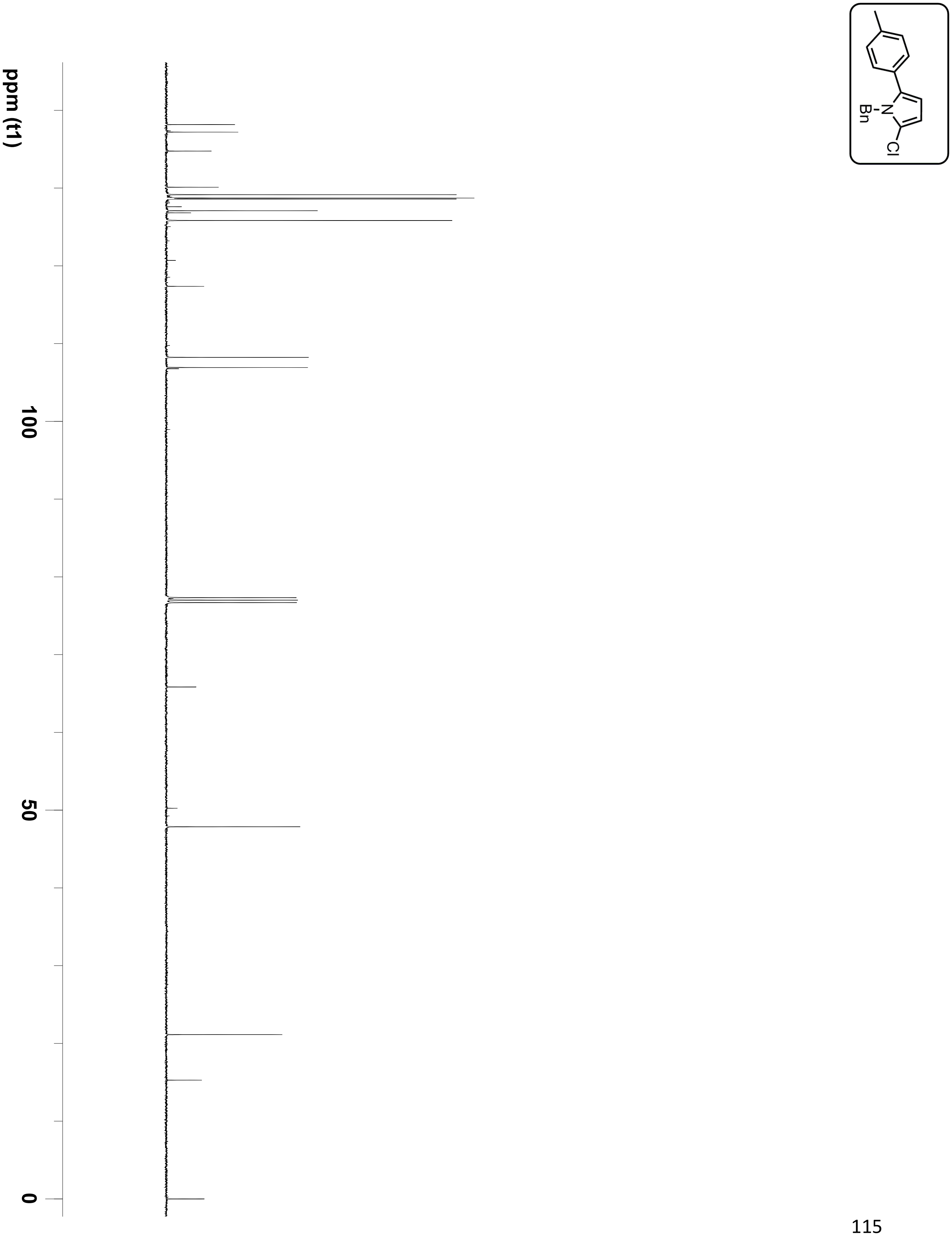
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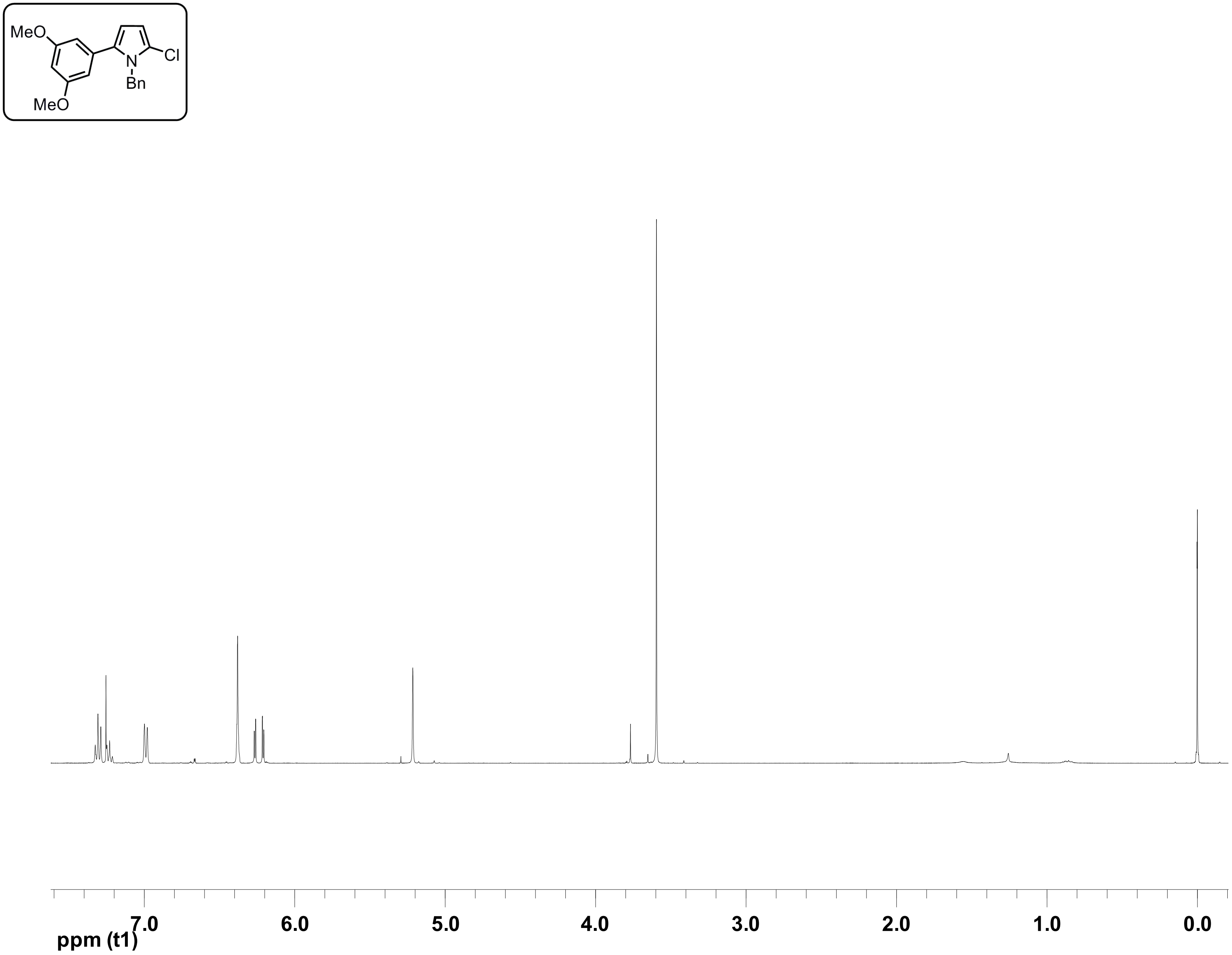
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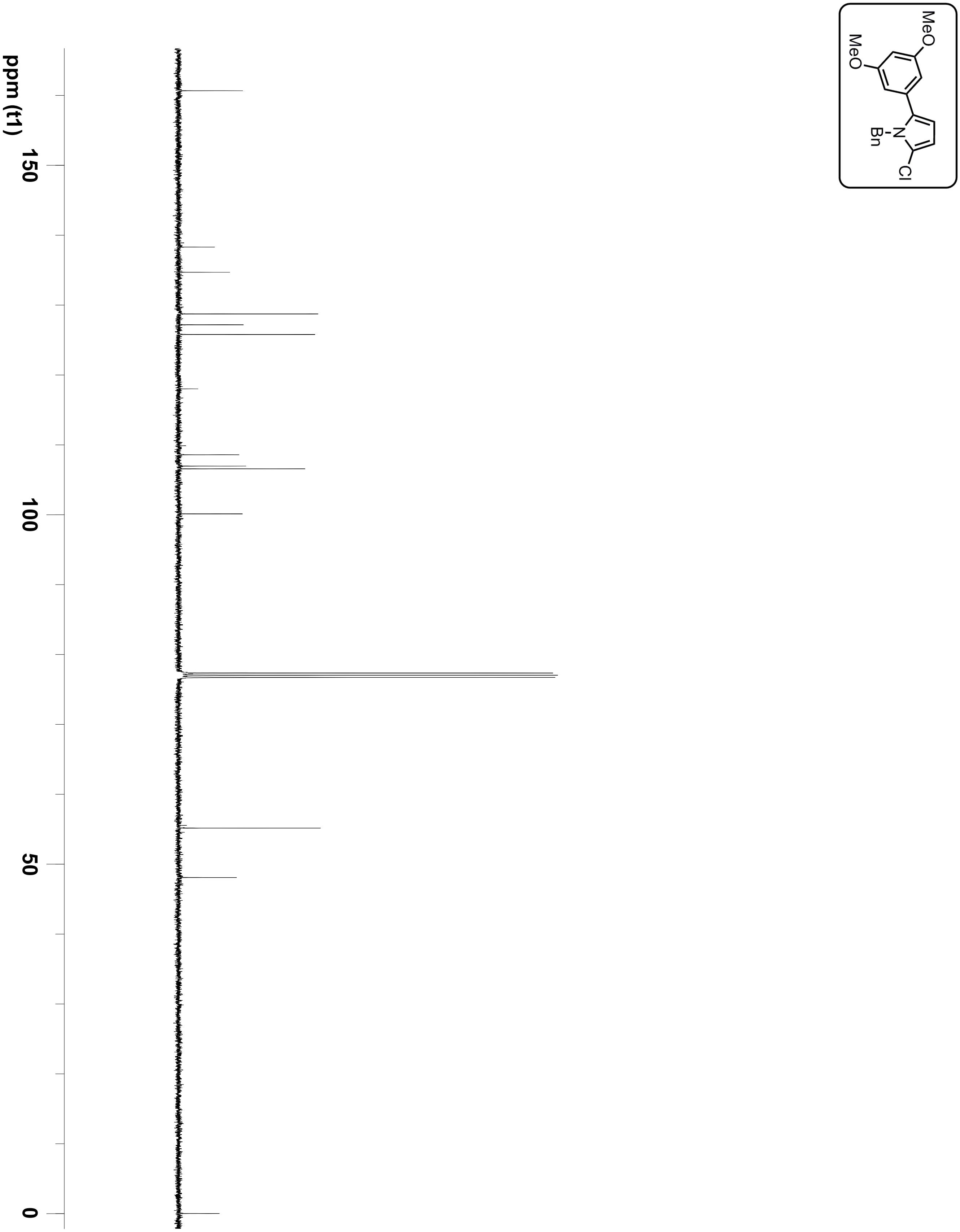
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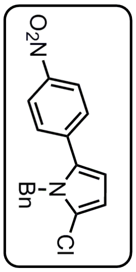
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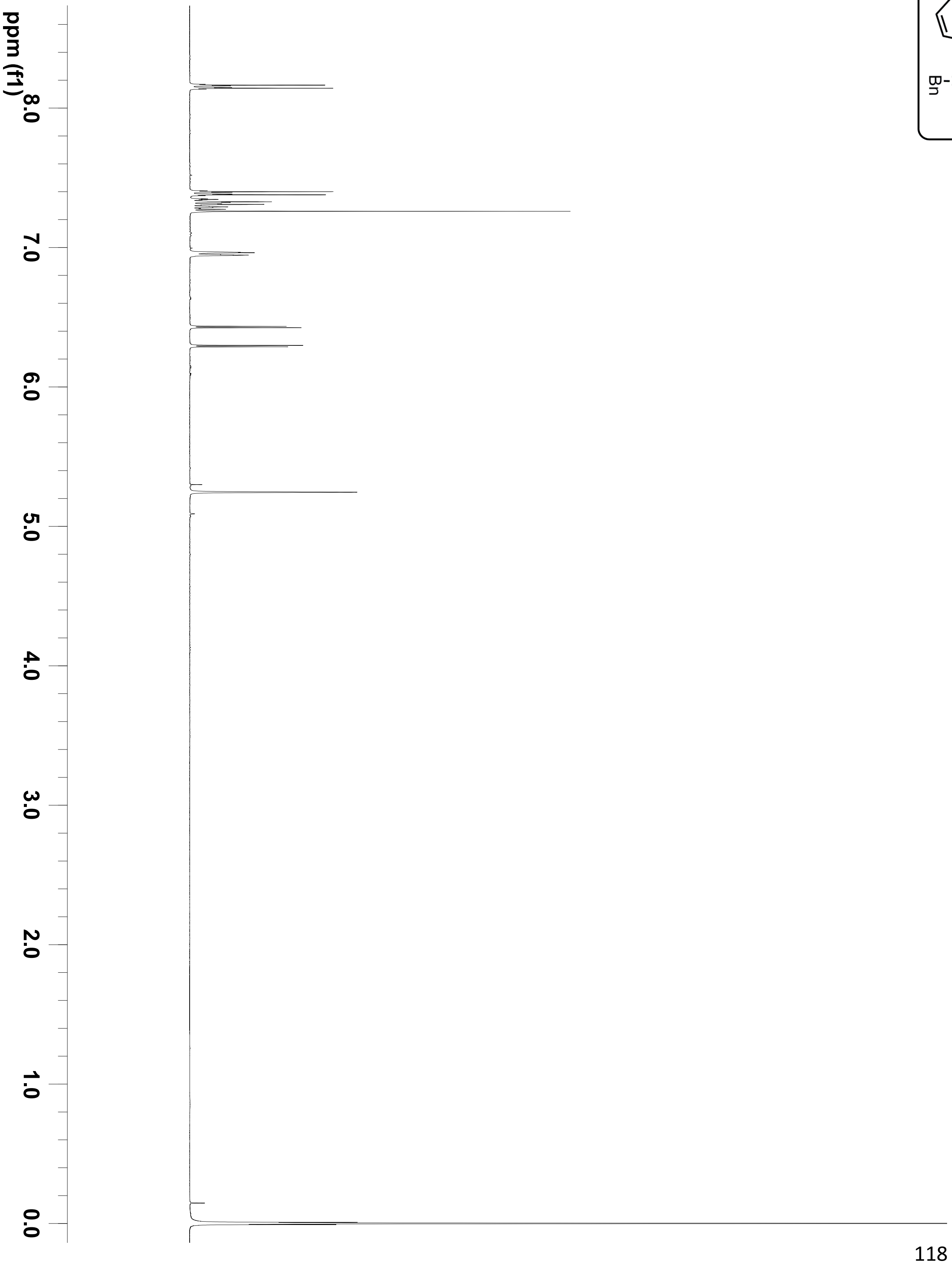
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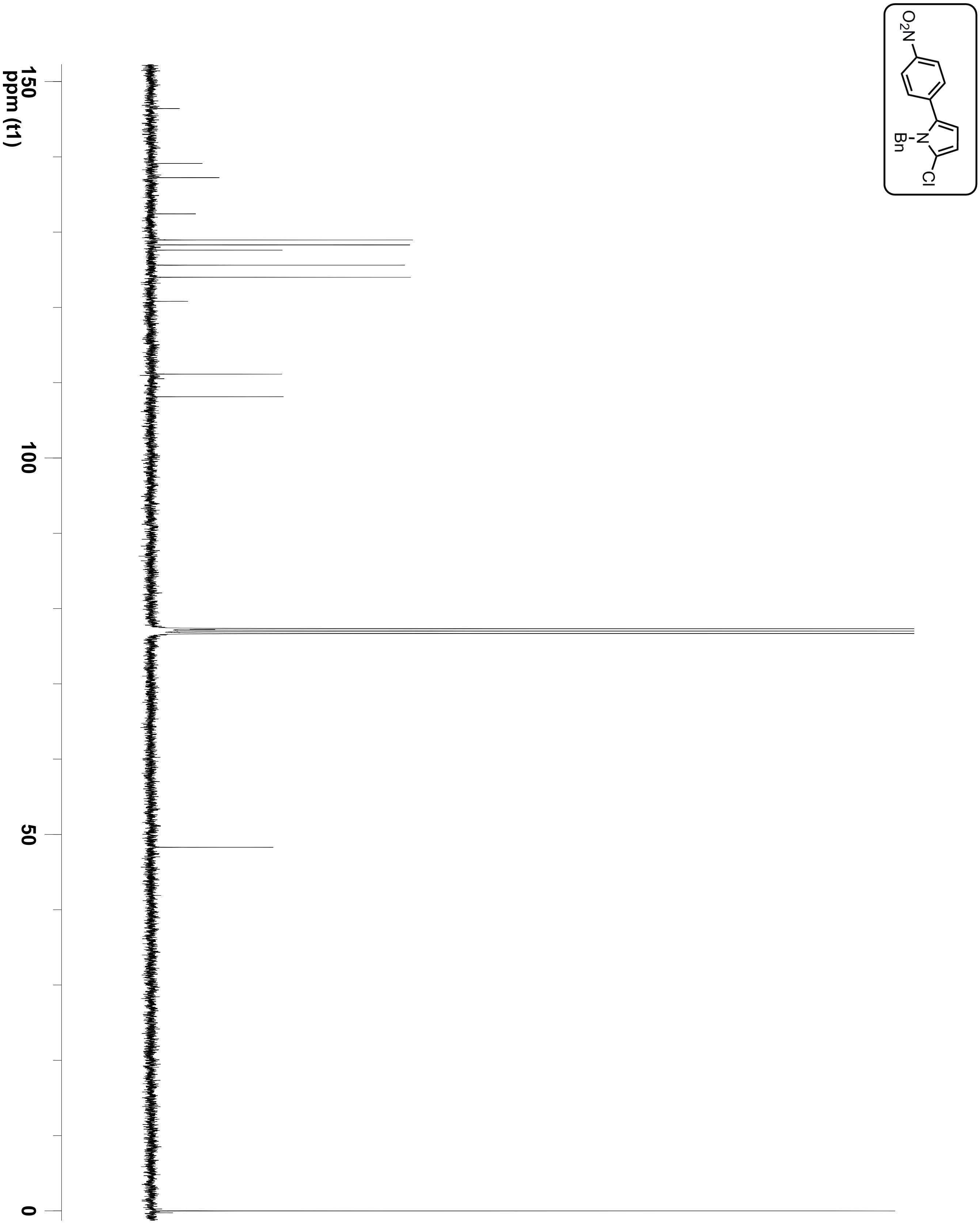

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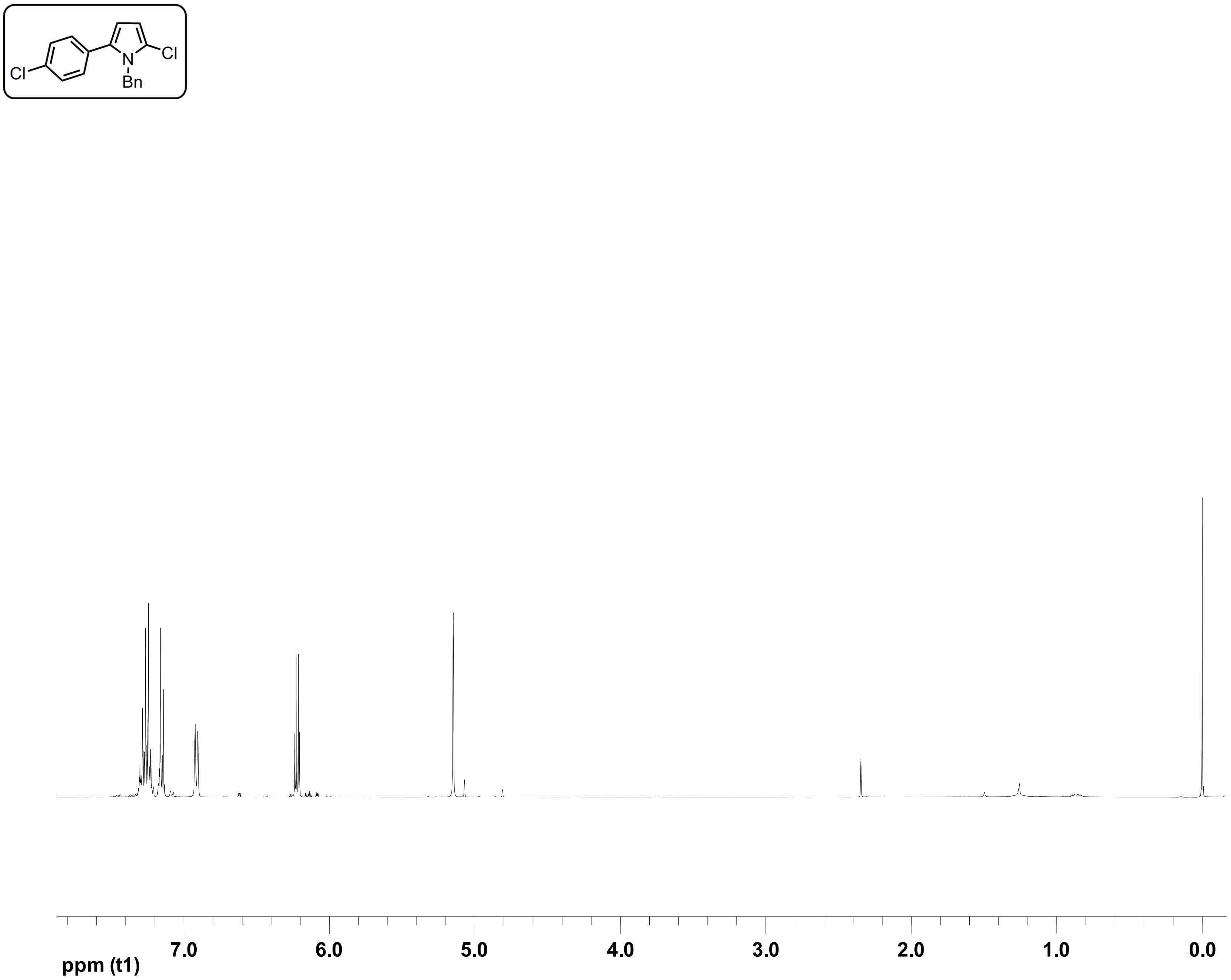
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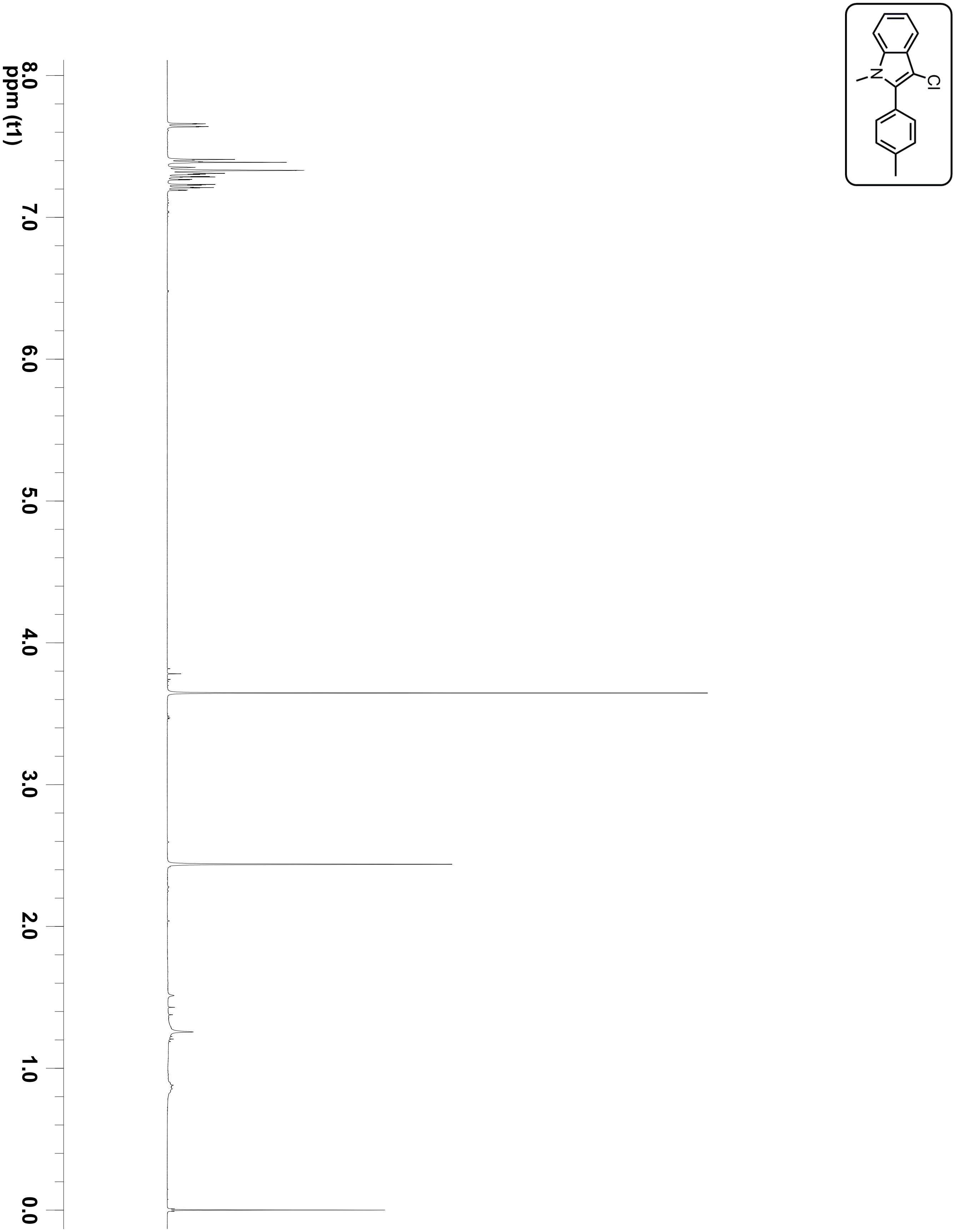
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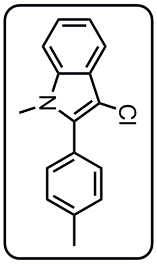
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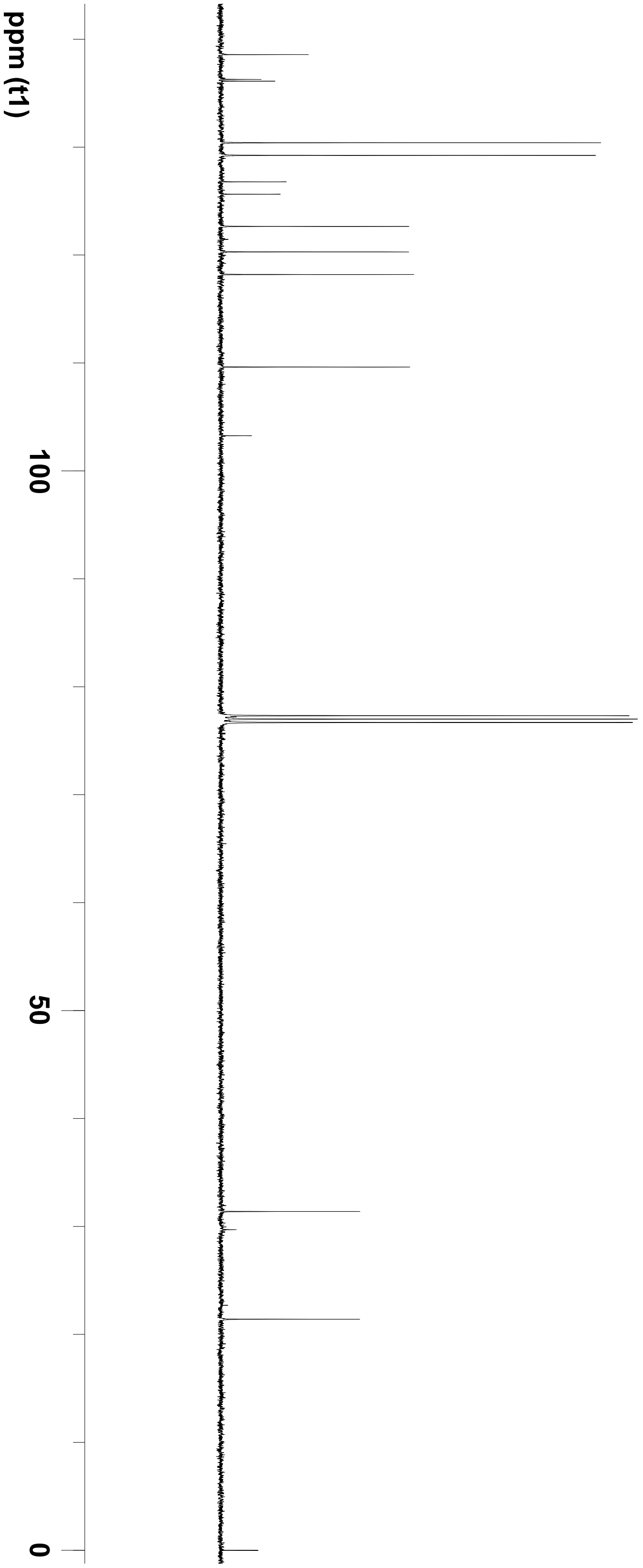
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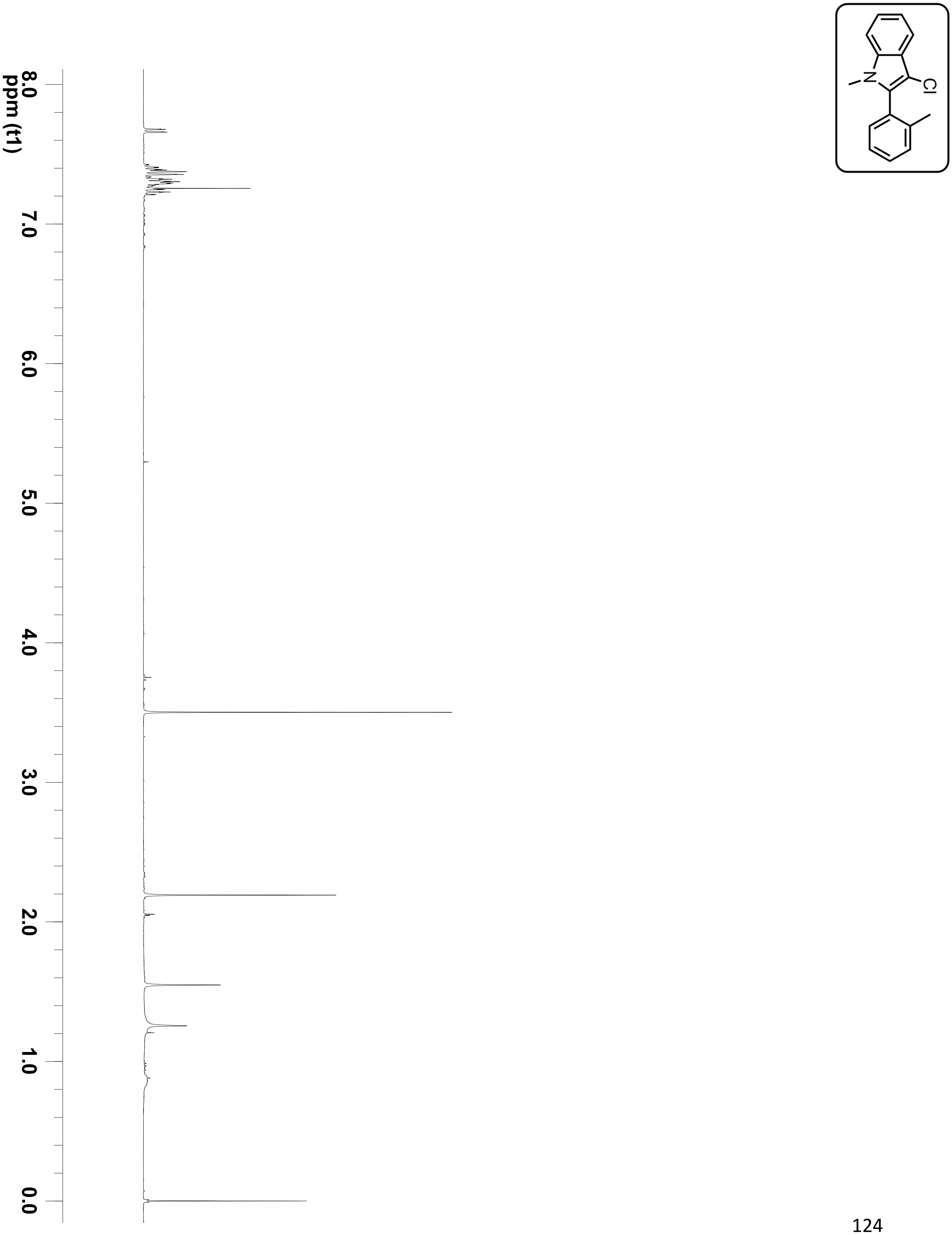
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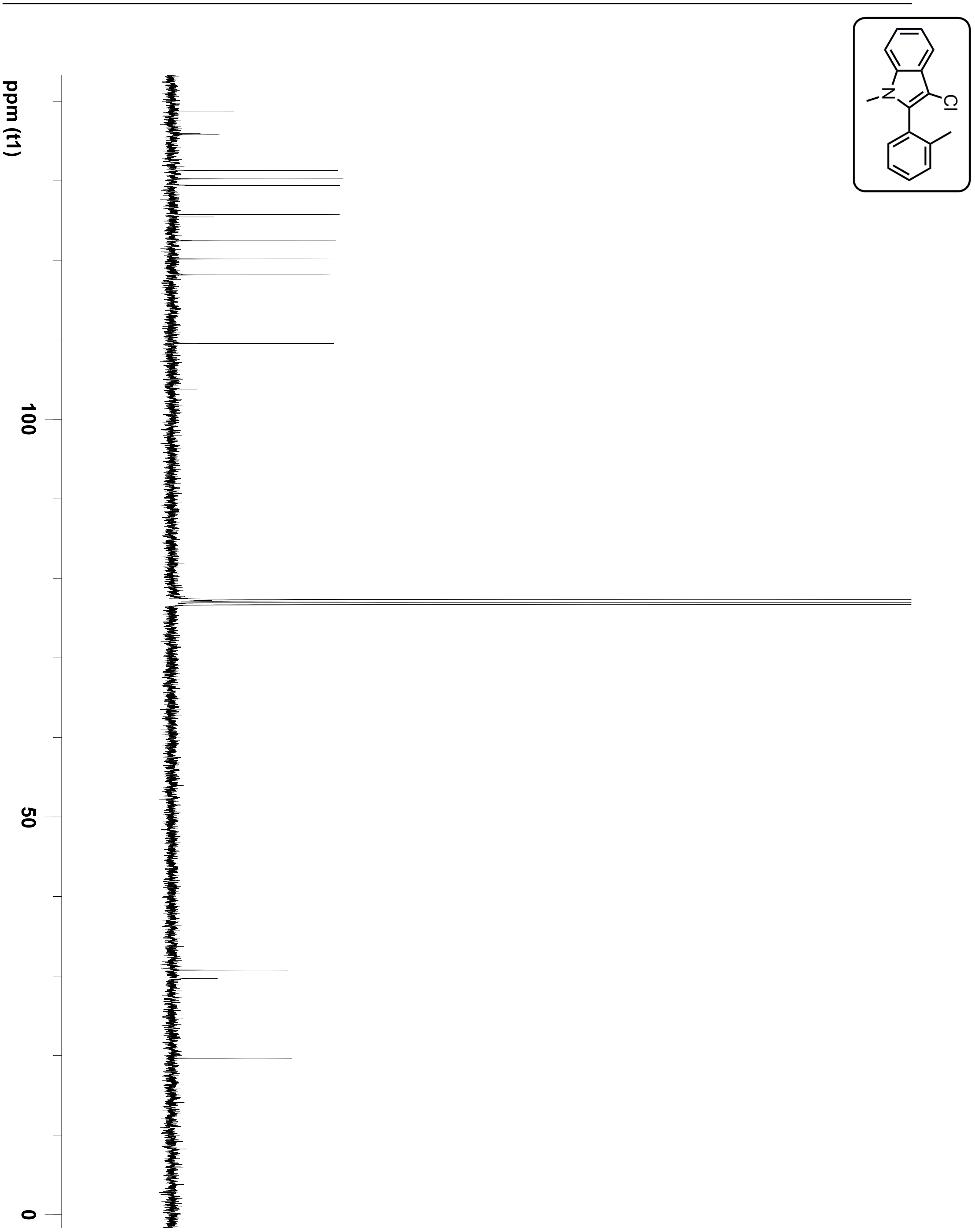
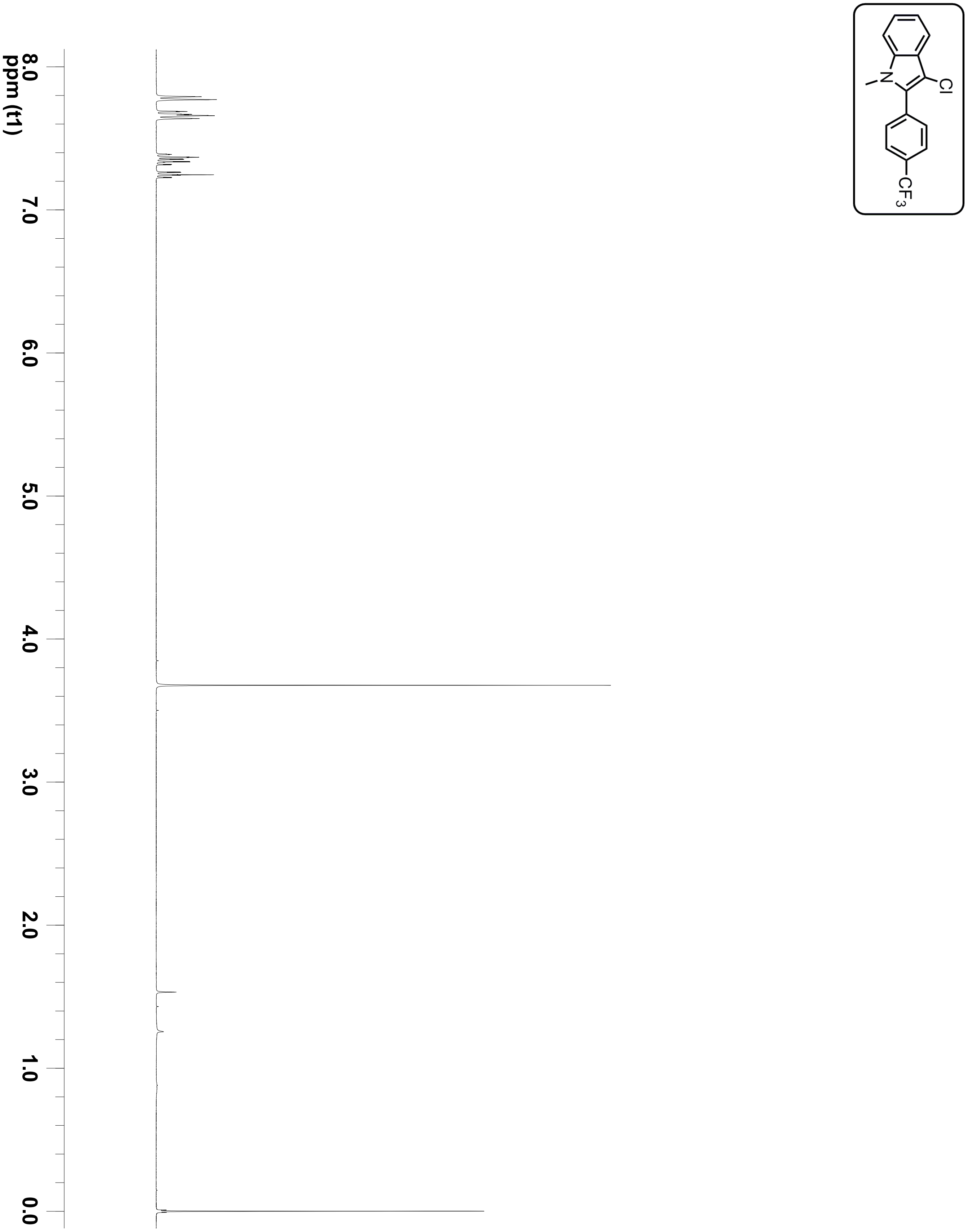
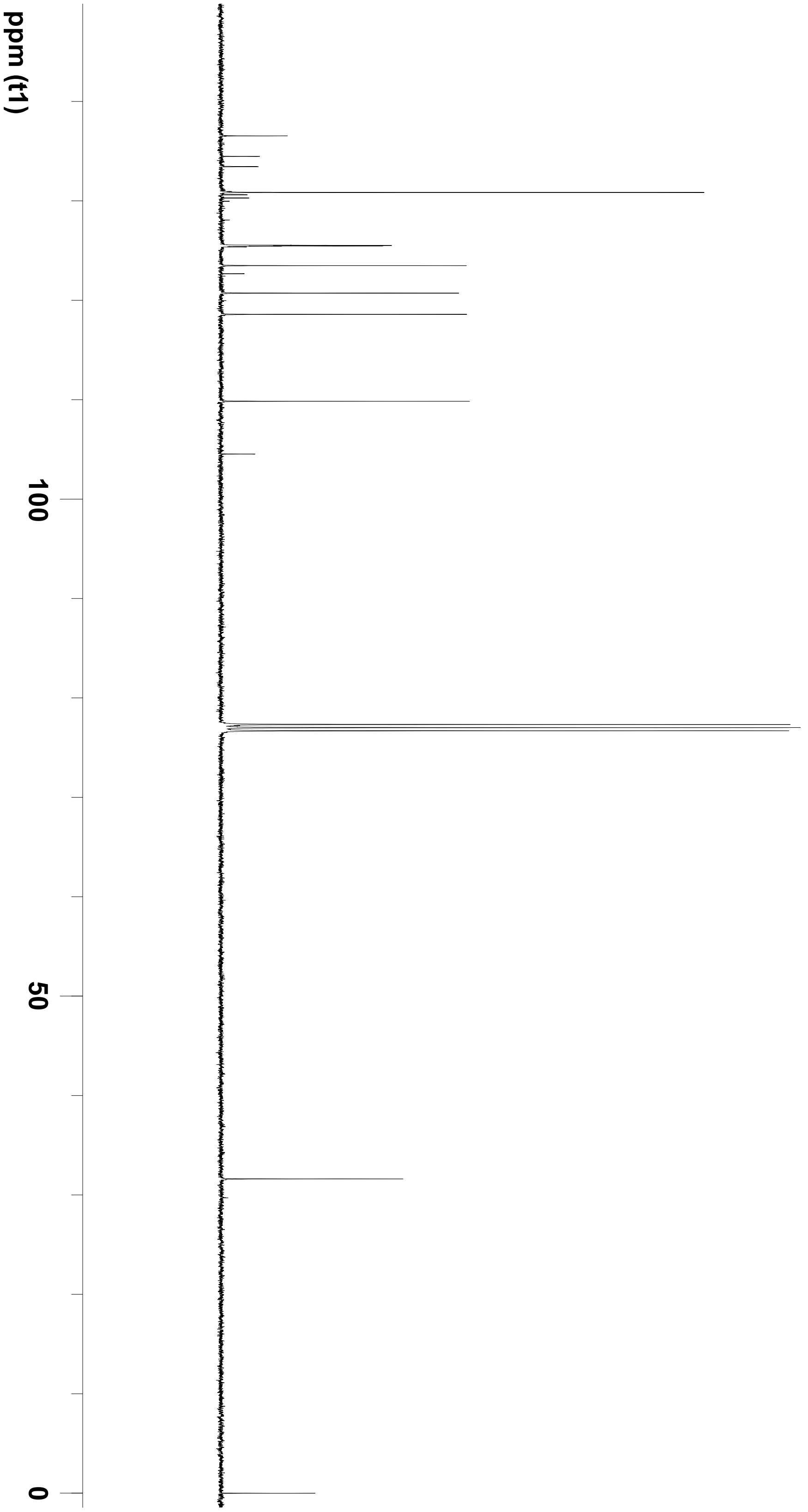
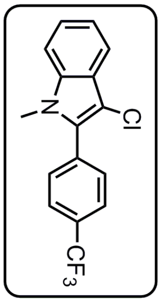
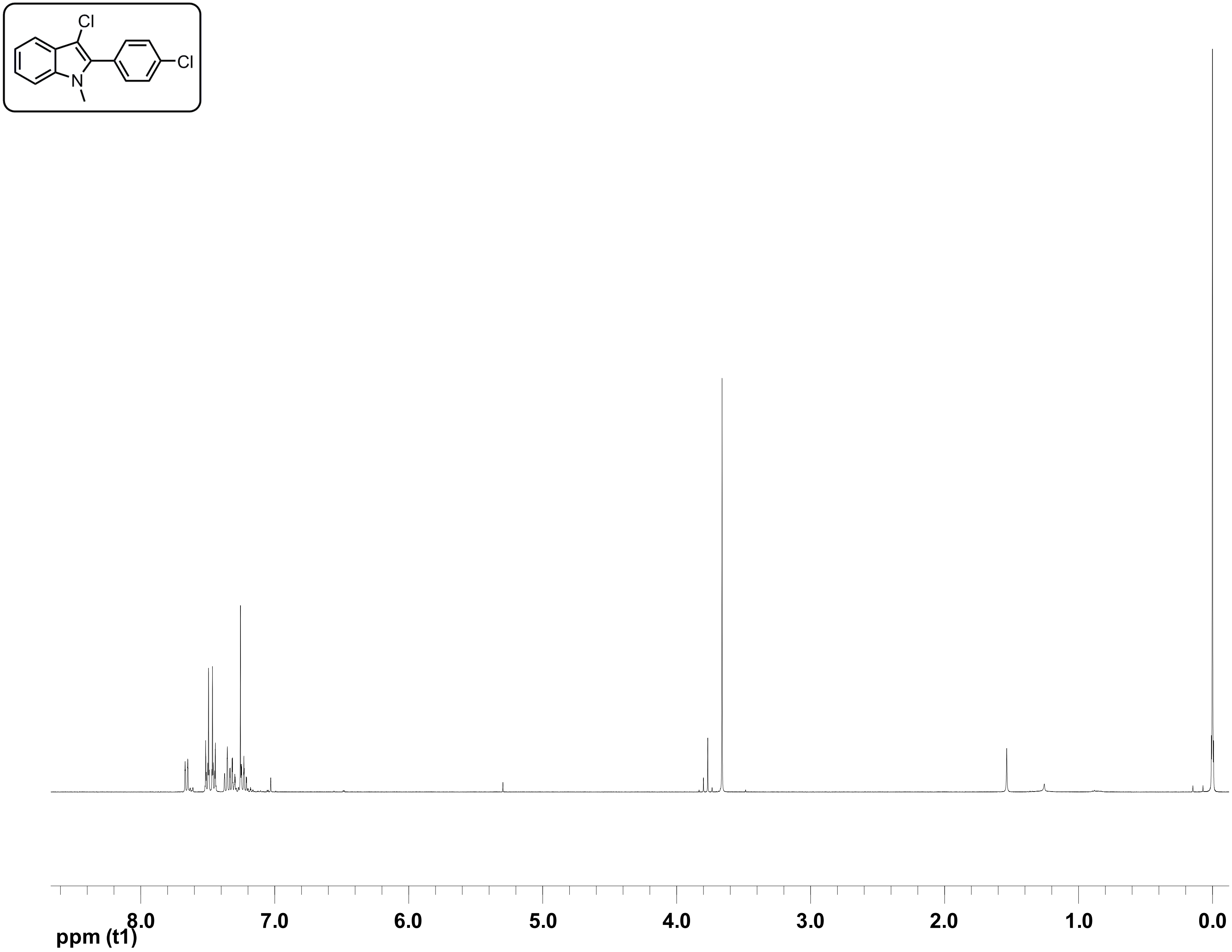
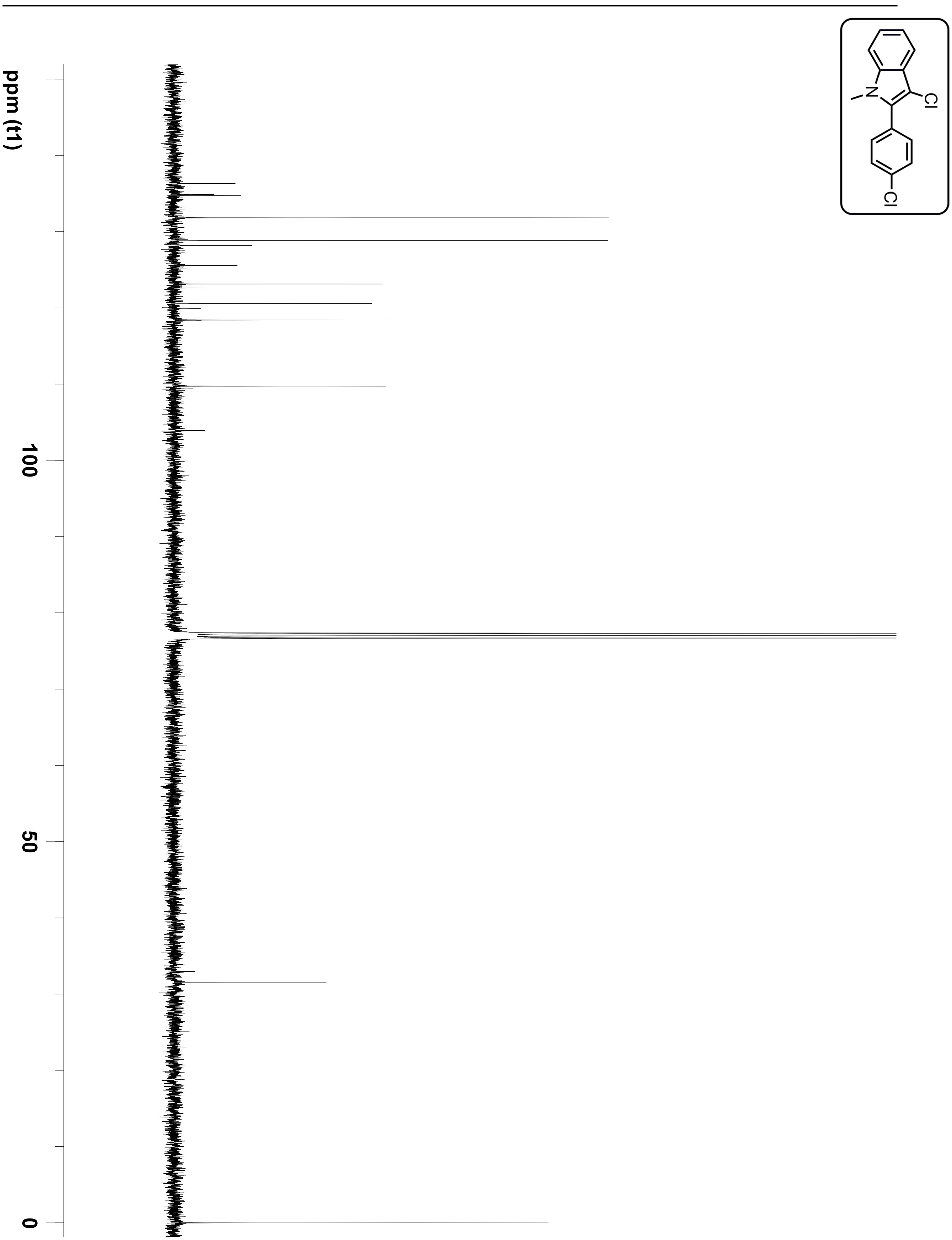

ppm (t1)
100
50
0
N
Cl

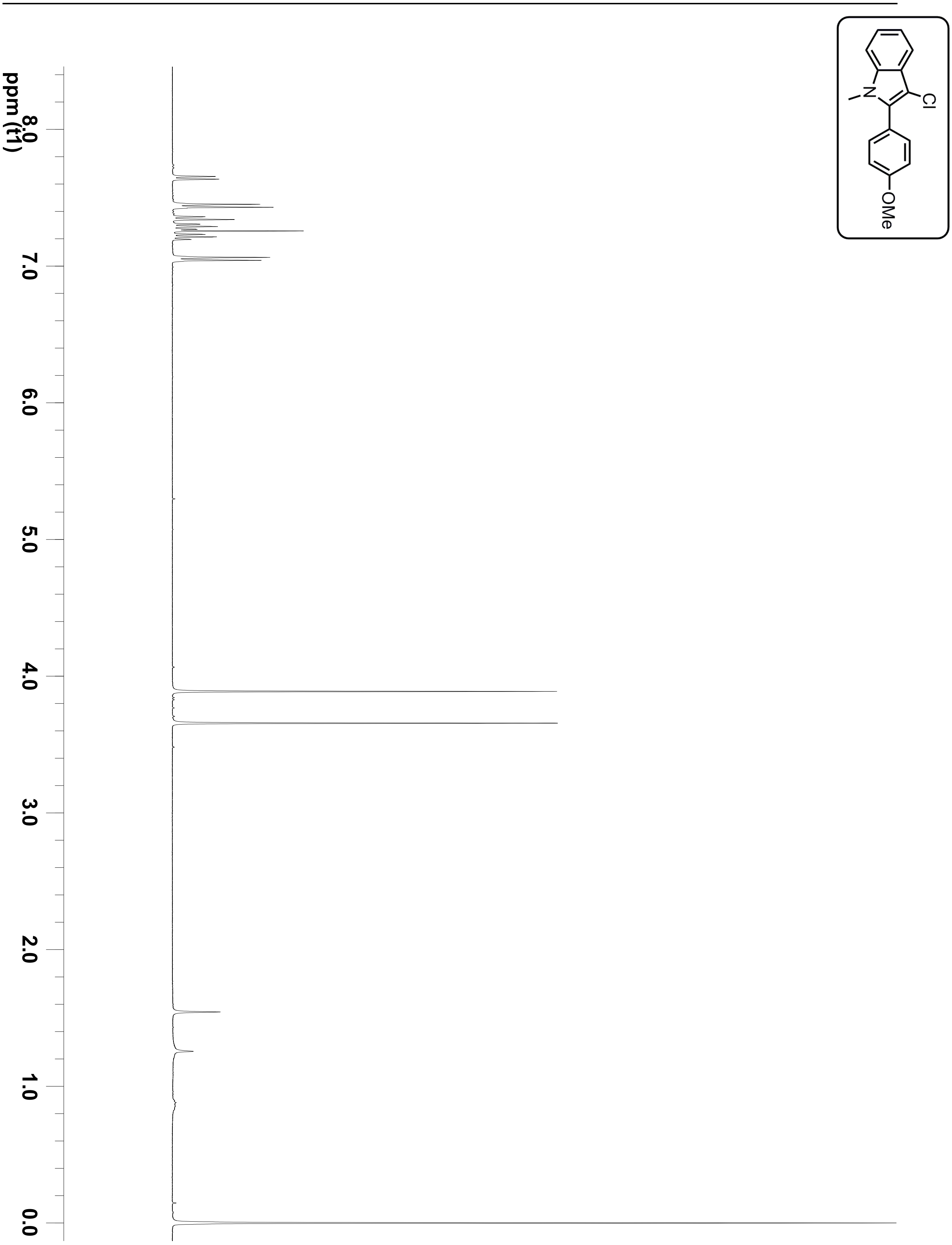

Cl
N
CF3
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

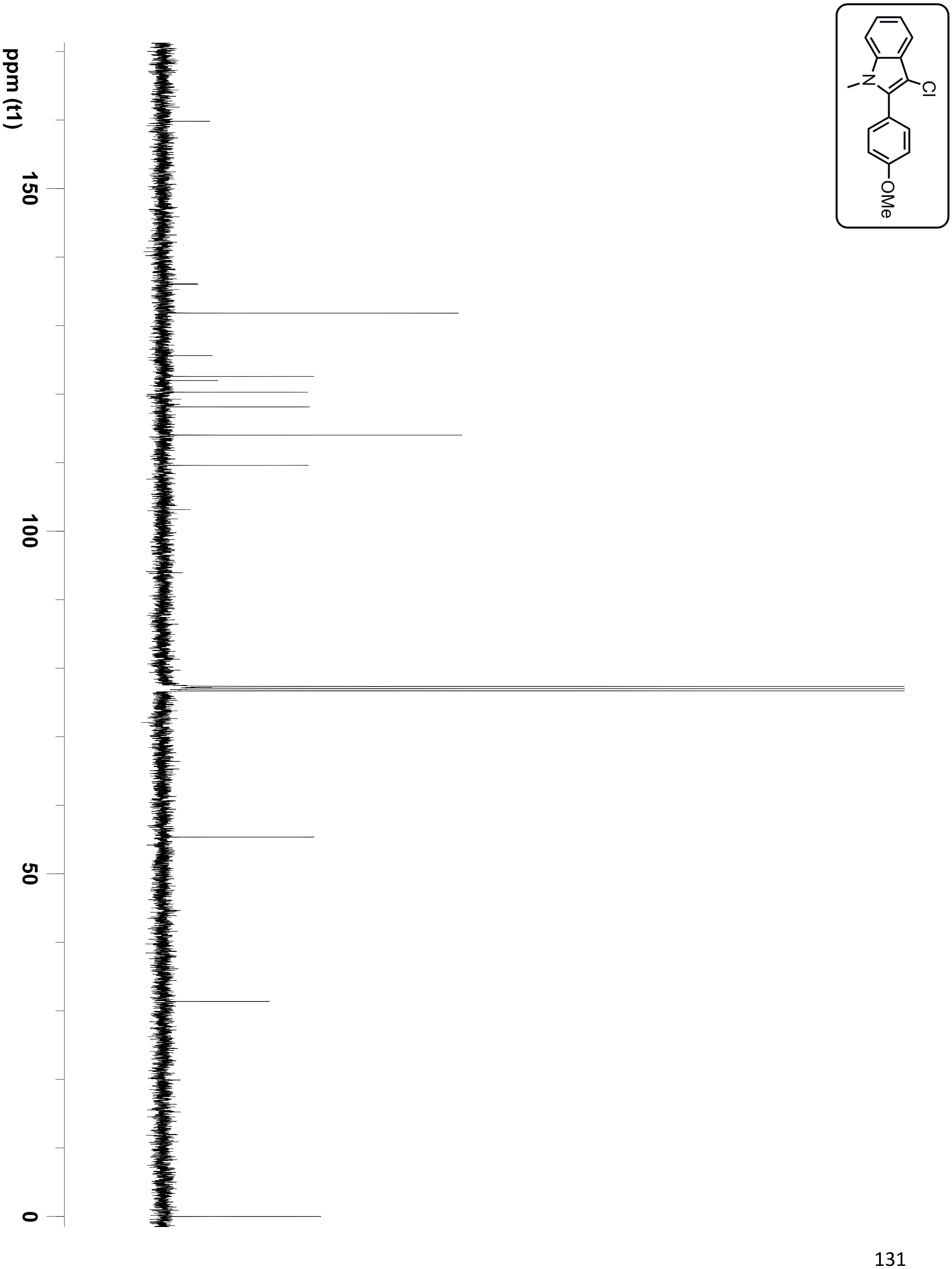

ppm (t1)
100
50
0

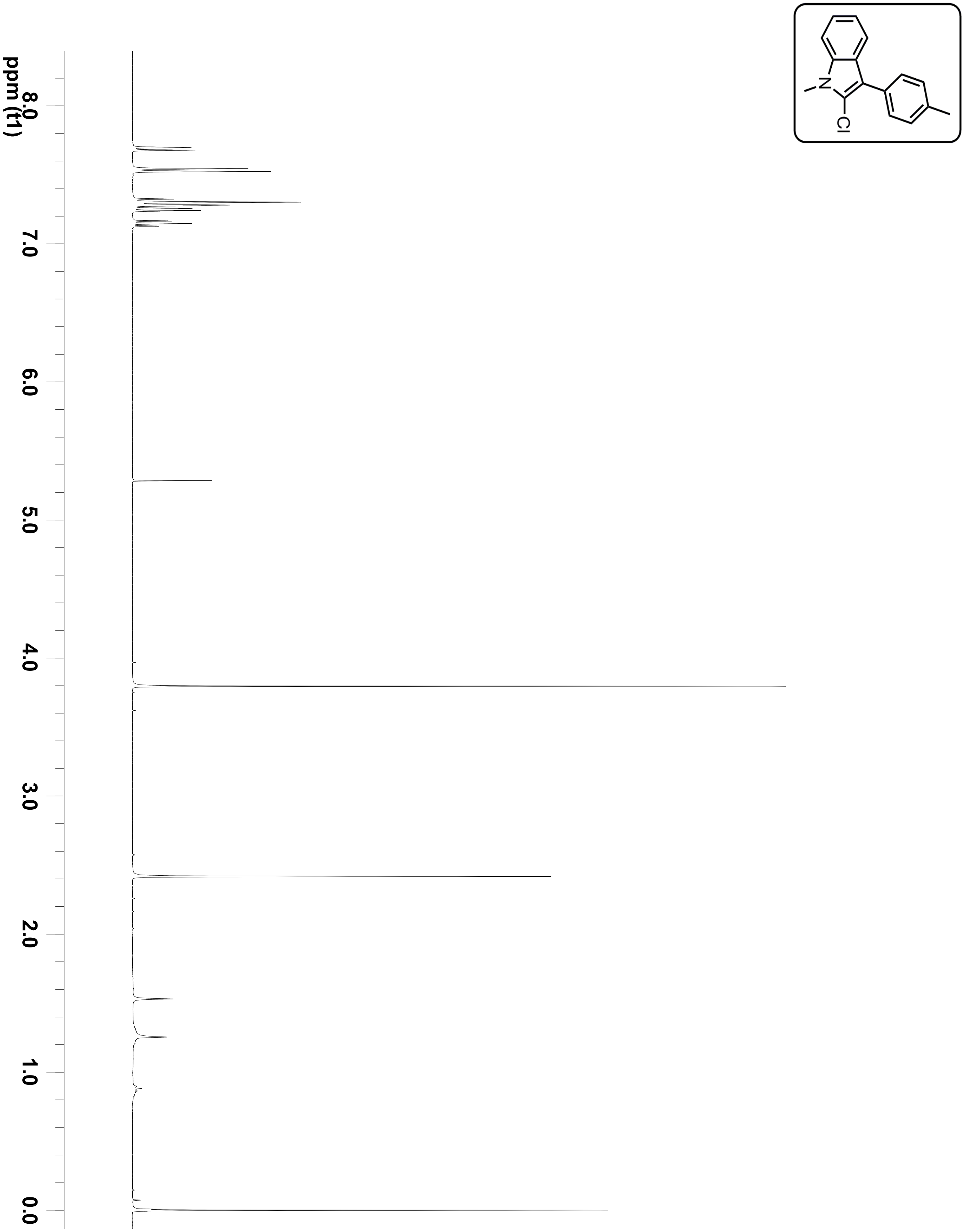

N
Cl
CF3

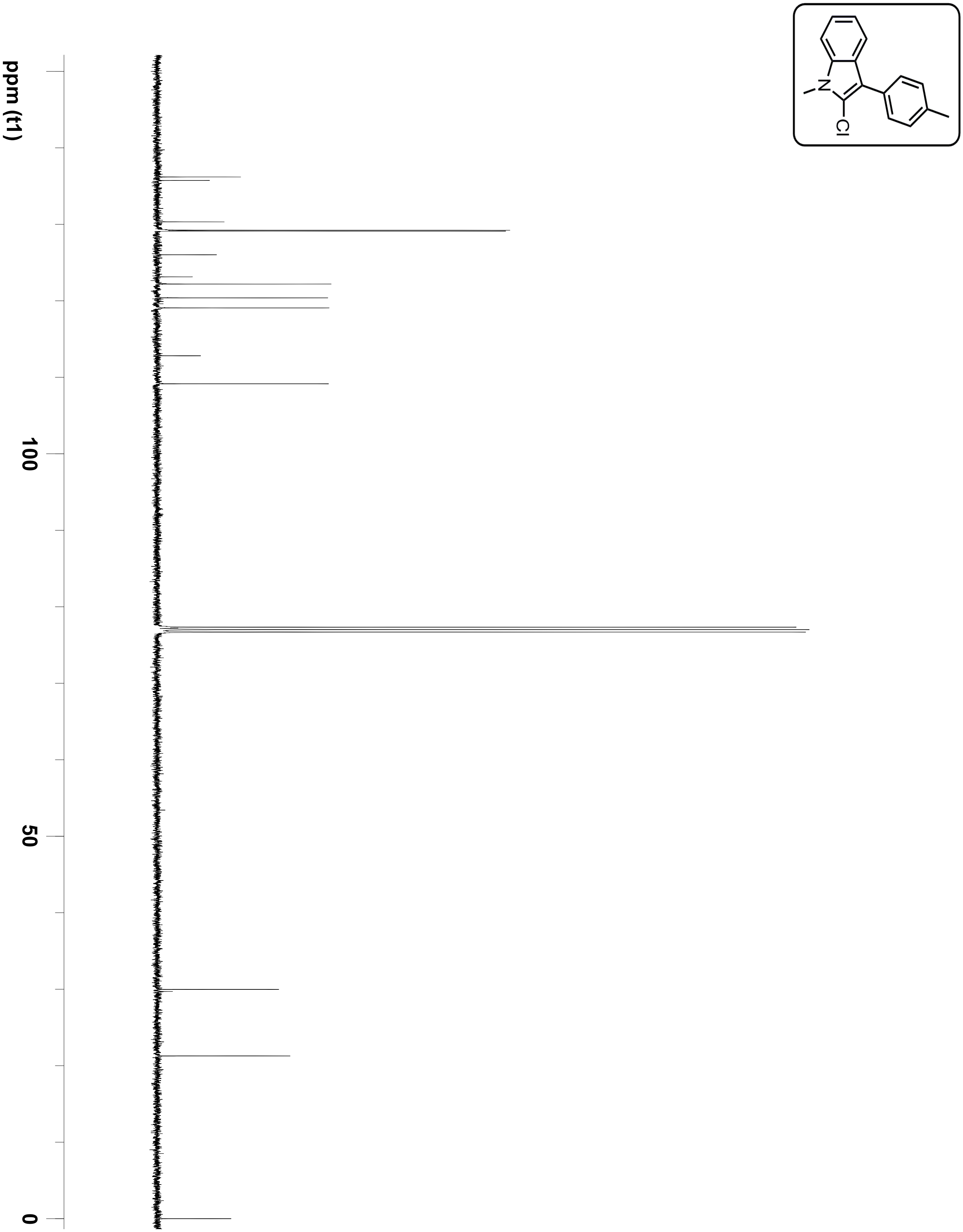

Cl
N
Cl
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

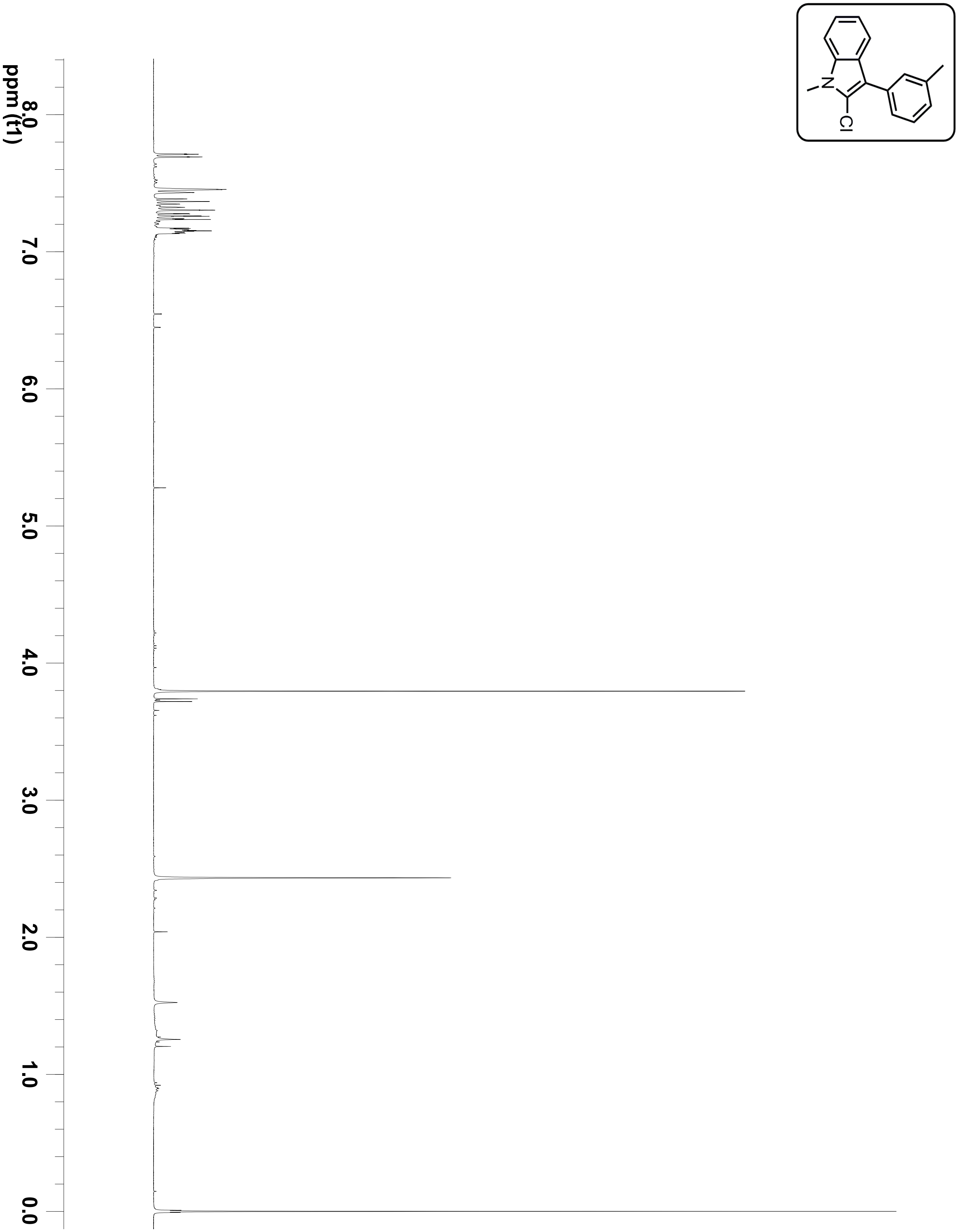

ppm (t1)
100
50
0
N
Cl
Cl

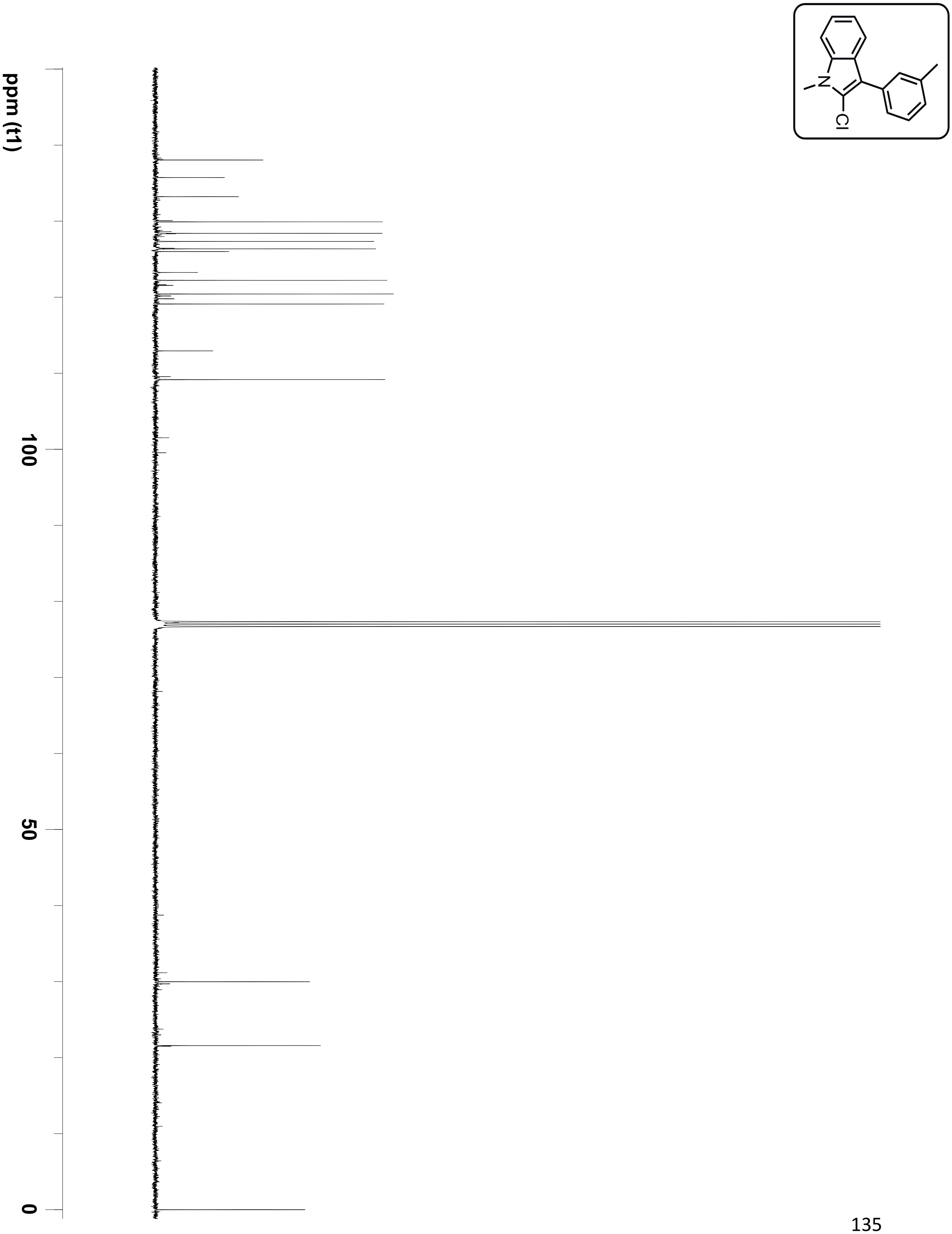

Cl
N
OMe
ppm (t1)
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

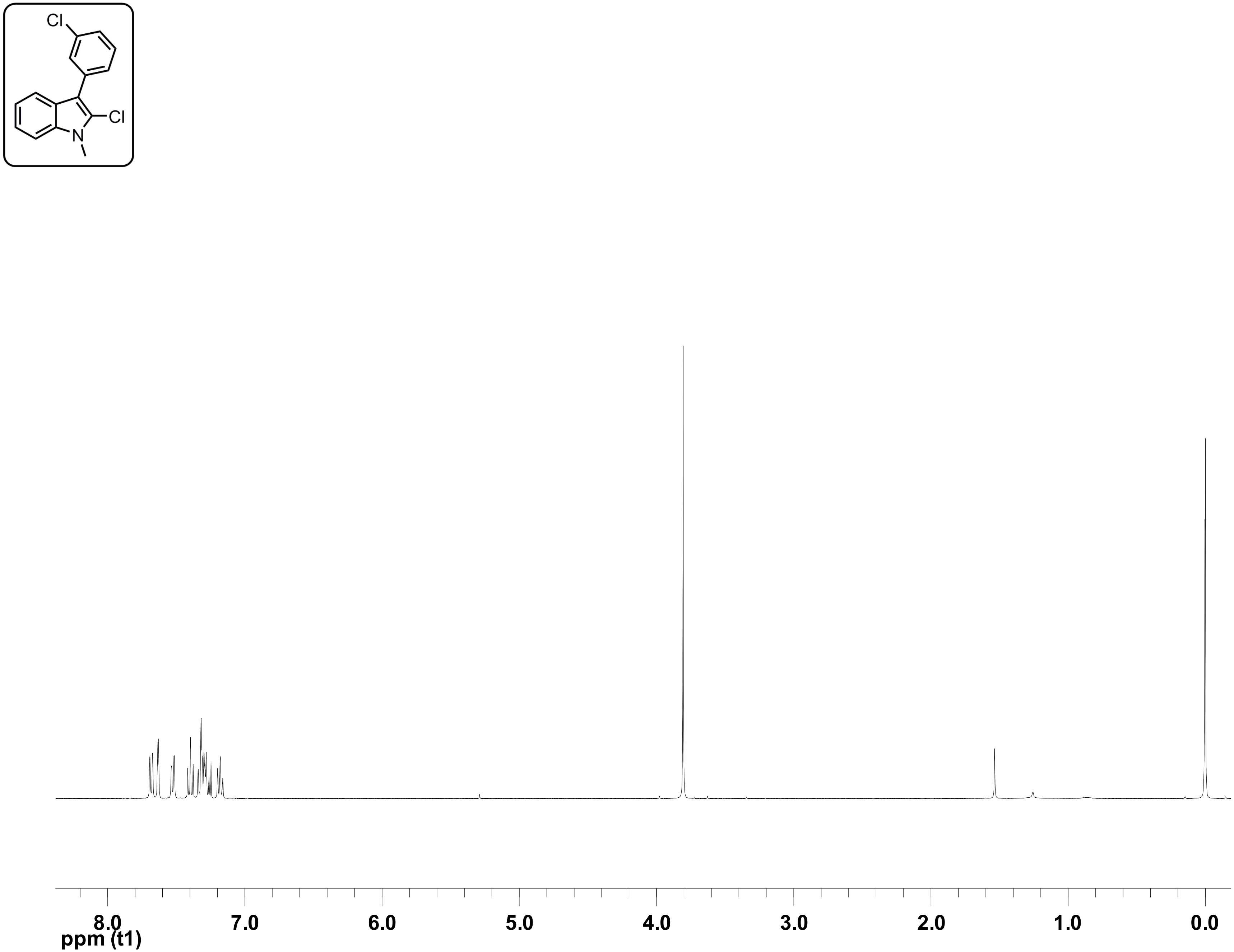

ppm (t1)
150
100
50
0
Cl
N
OMe

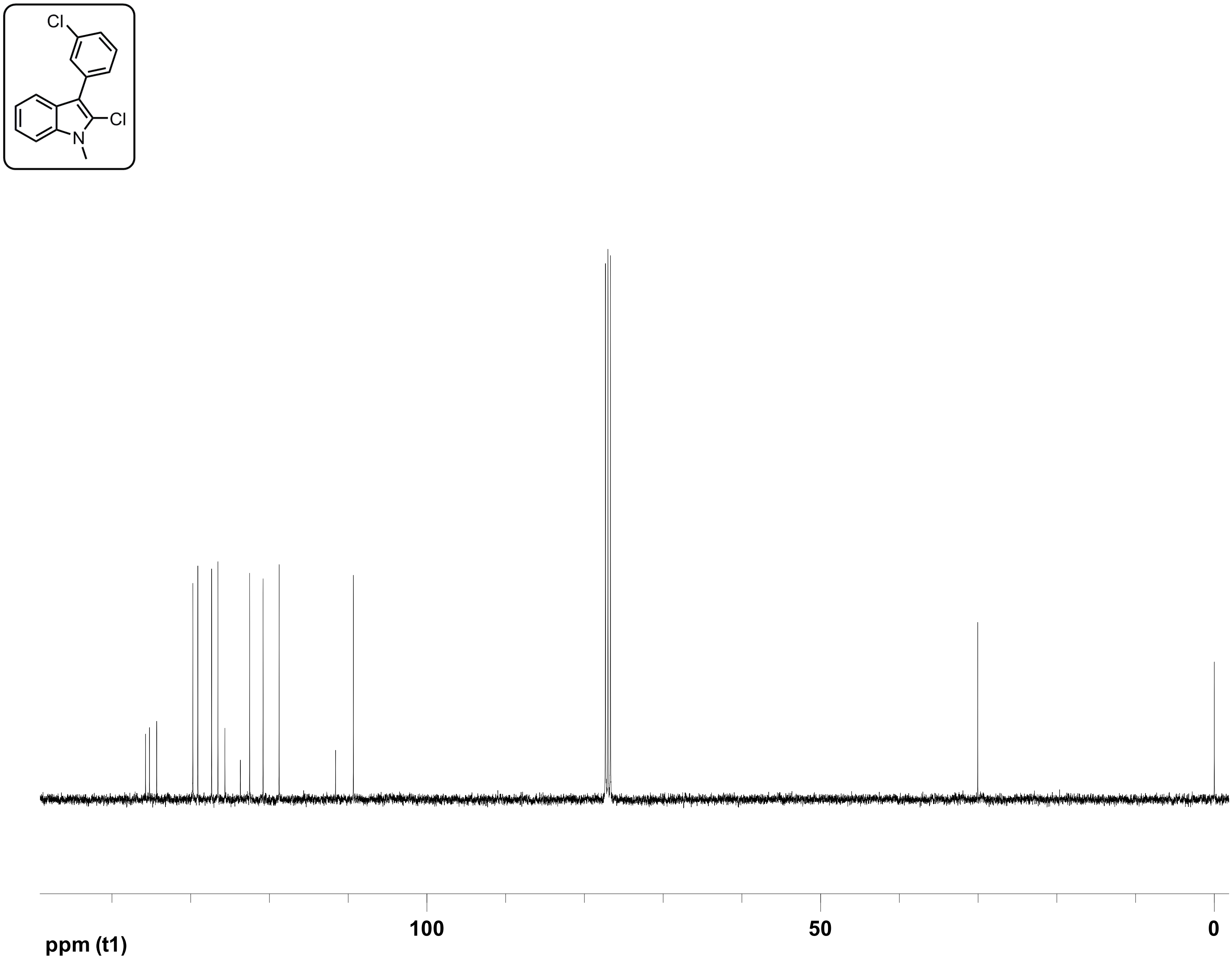

ppm (t1)
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
N
Cl

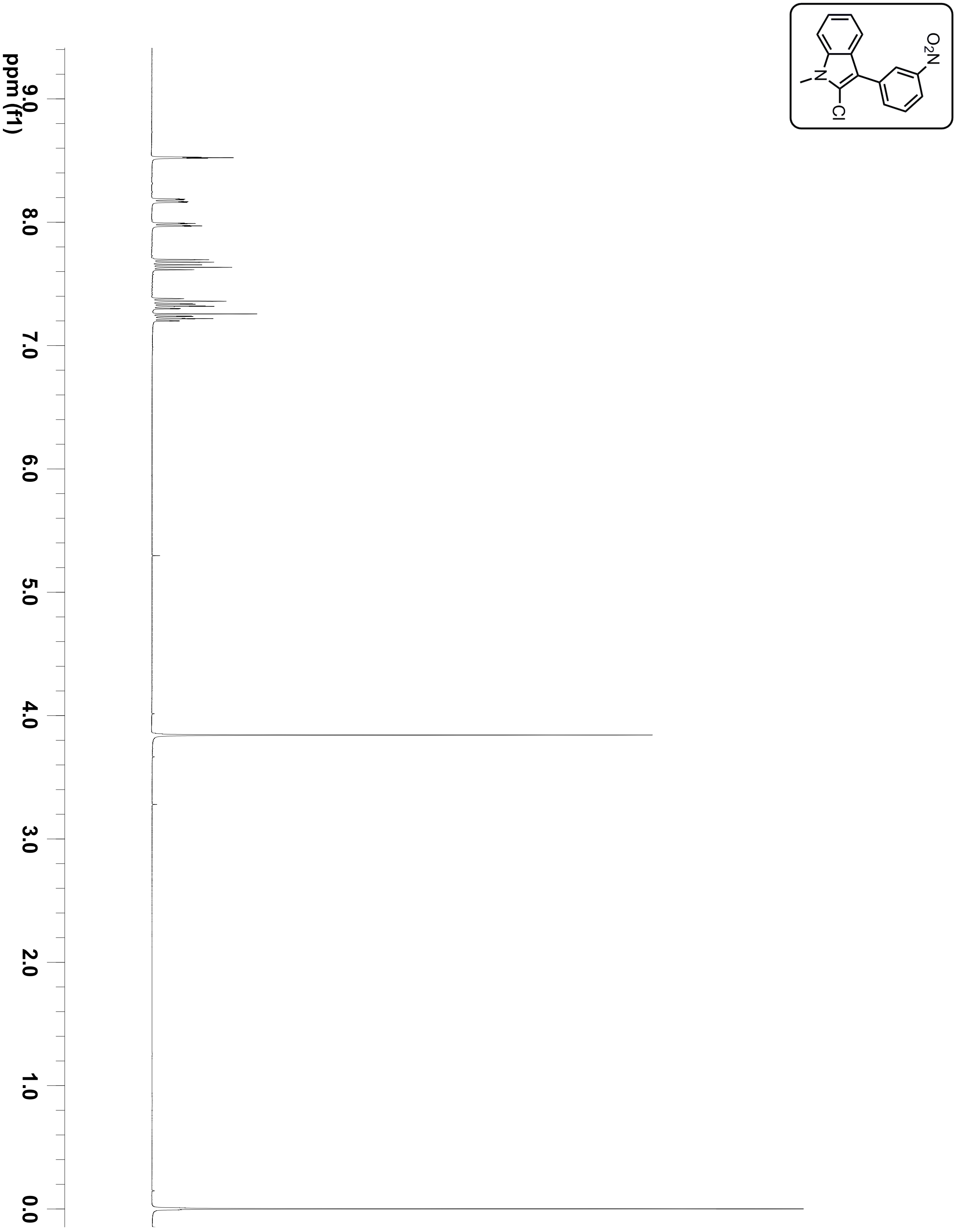

ppm (t1)
100
50
0
N
Cl

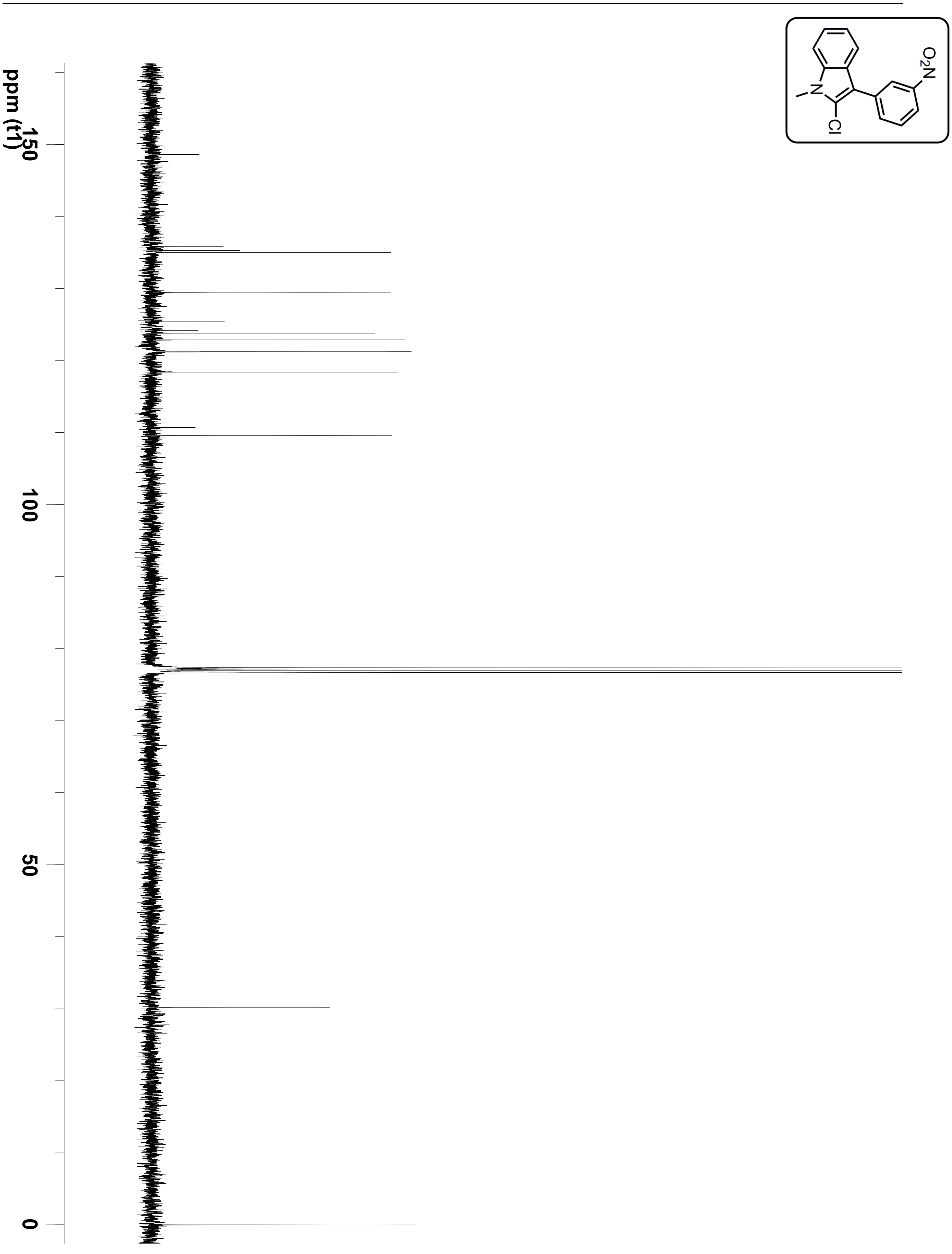

ppm (t1)
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
N
Cl

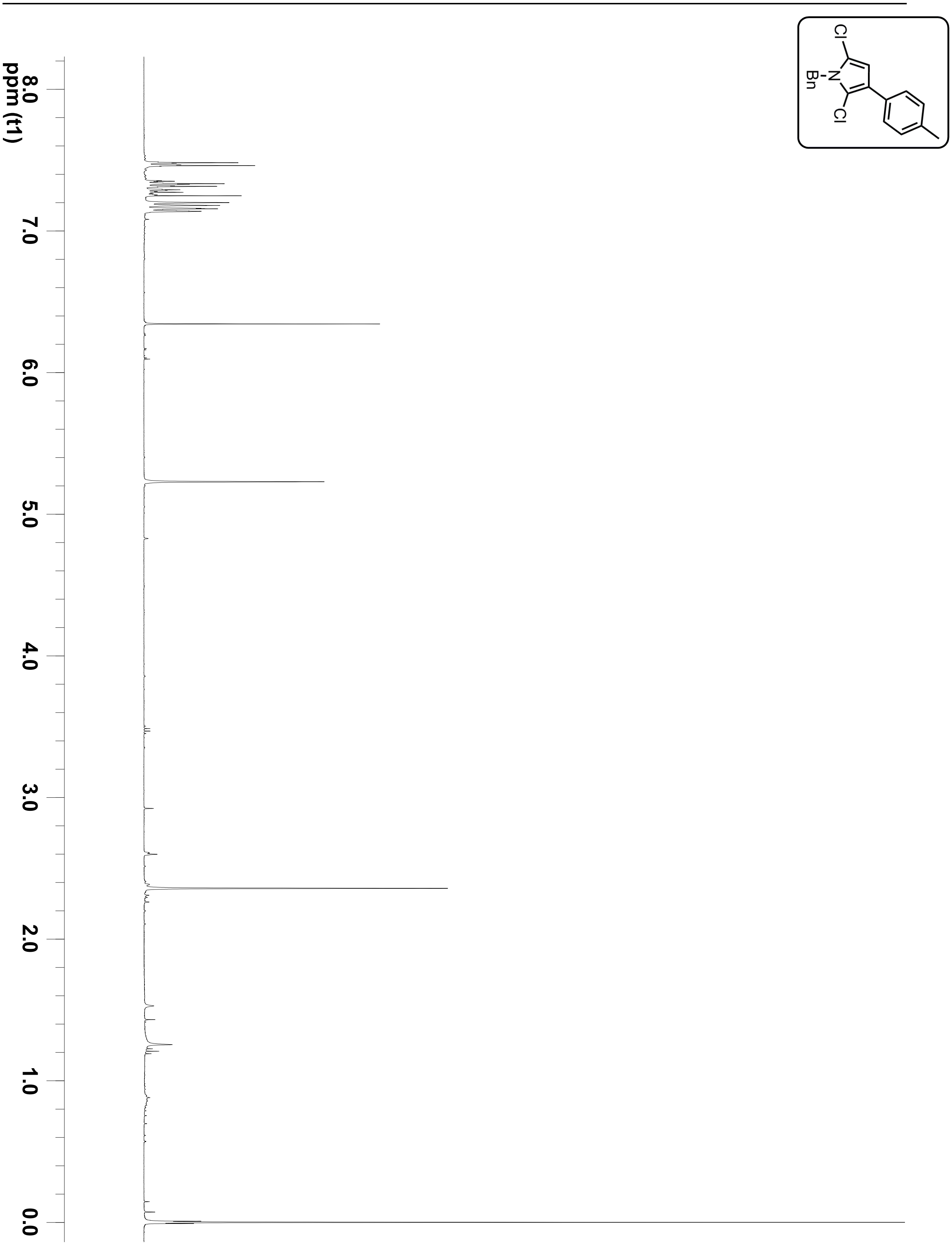

ppm (t1)
100
50
0
N
Cl


Cl
Cl
N
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

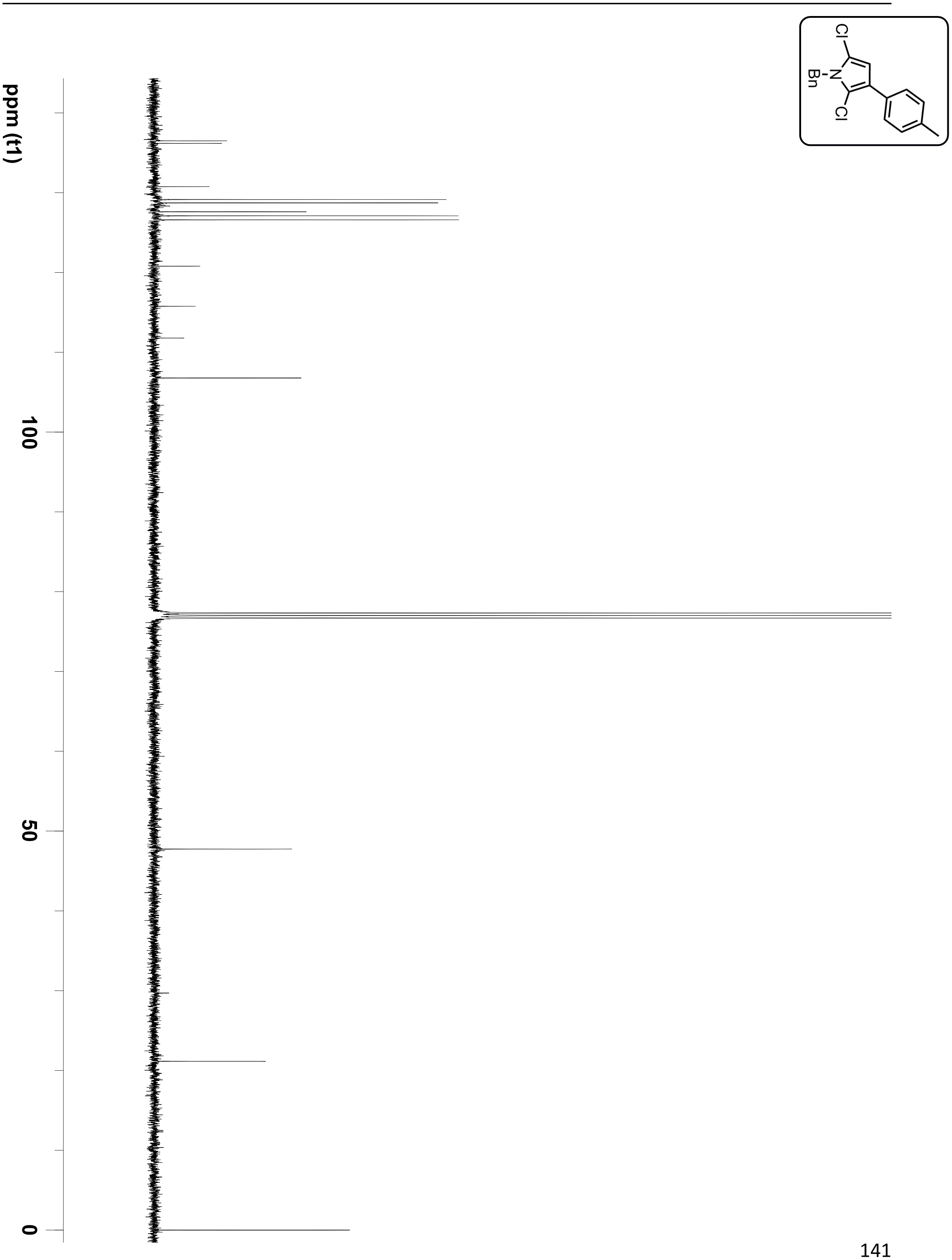

Cl
Cl
N
ppm (t1)
100
50
0

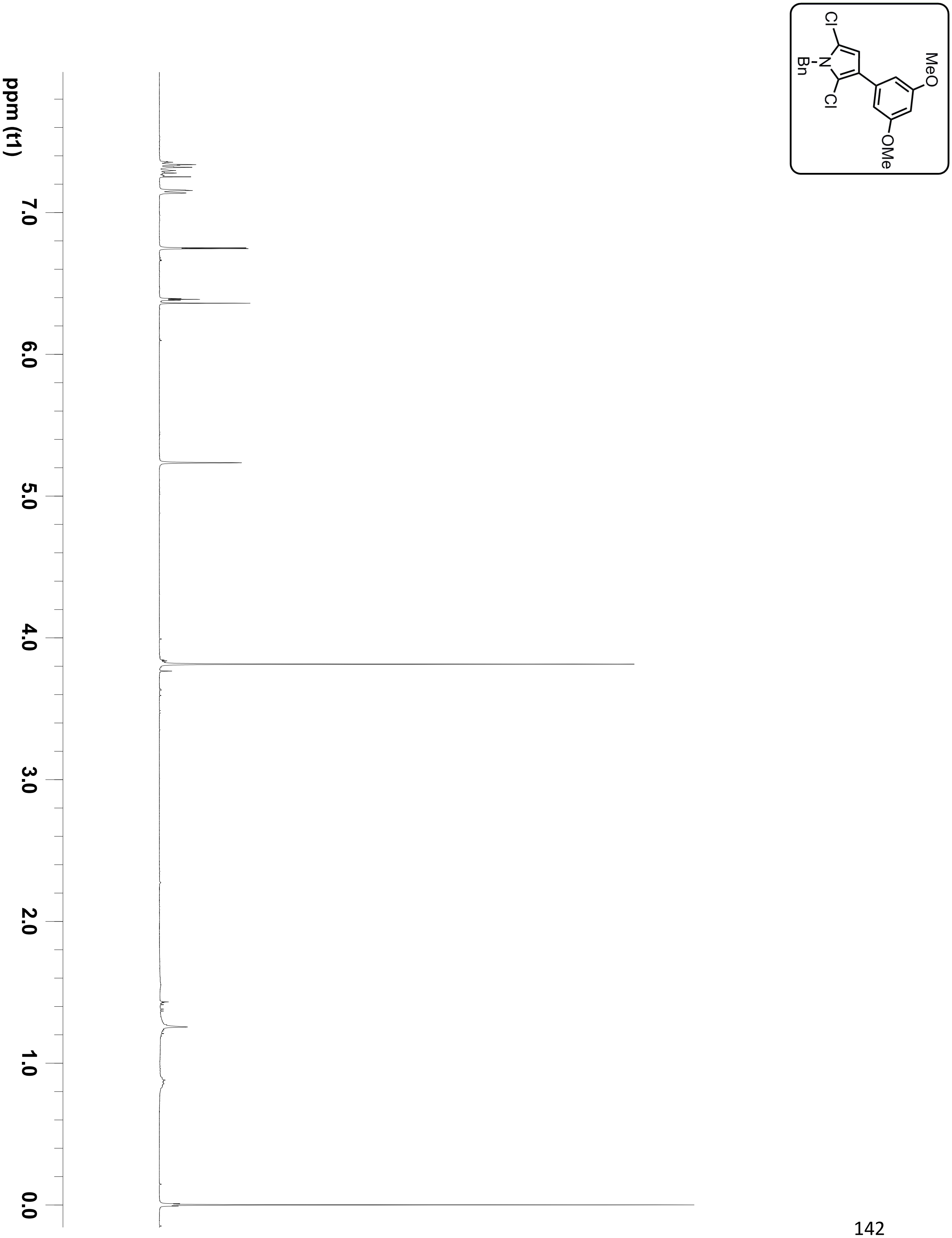

O2N
N
Cl
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)

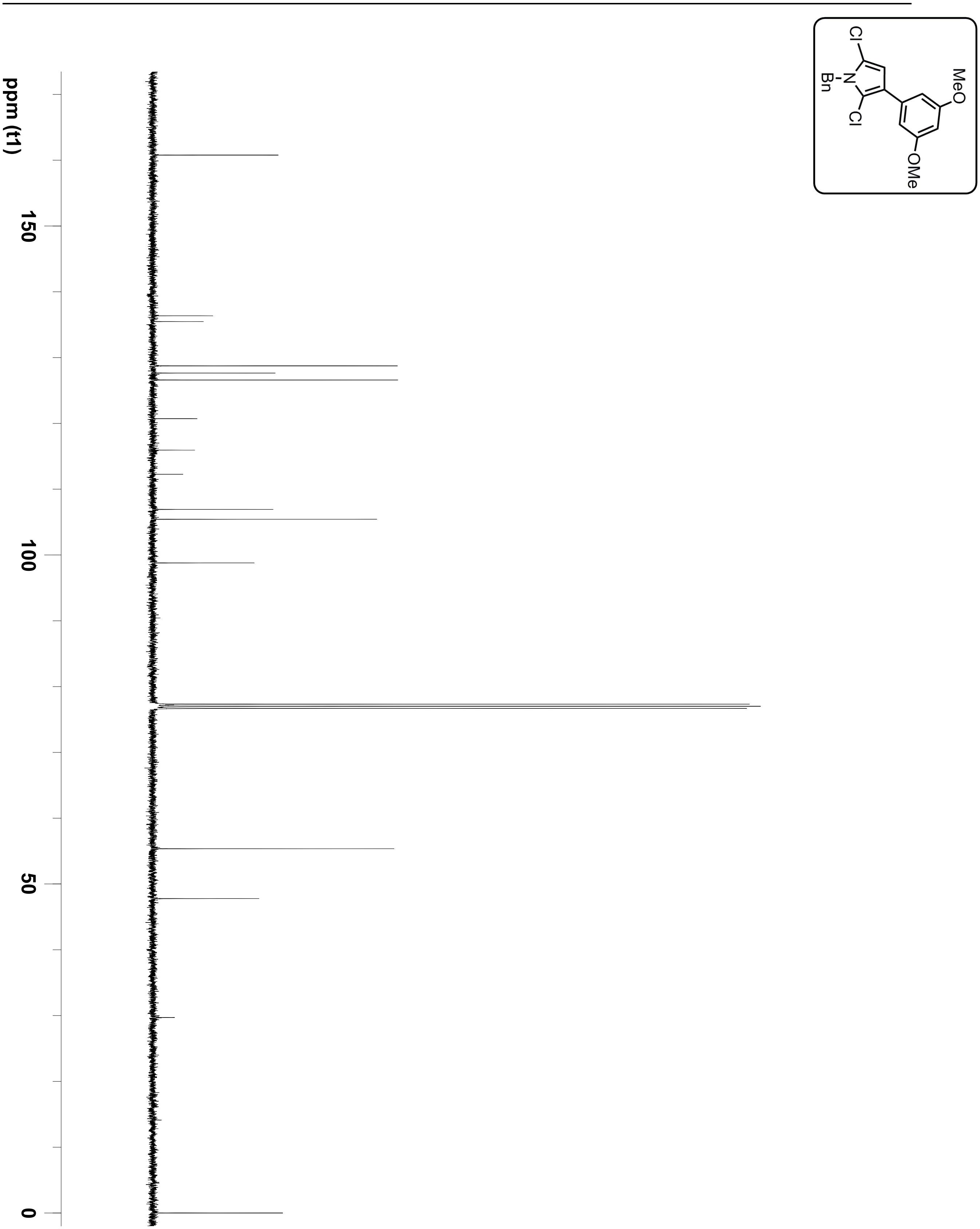

ppm (t1)
150
100
50
0
O$_2$N
N
Cl



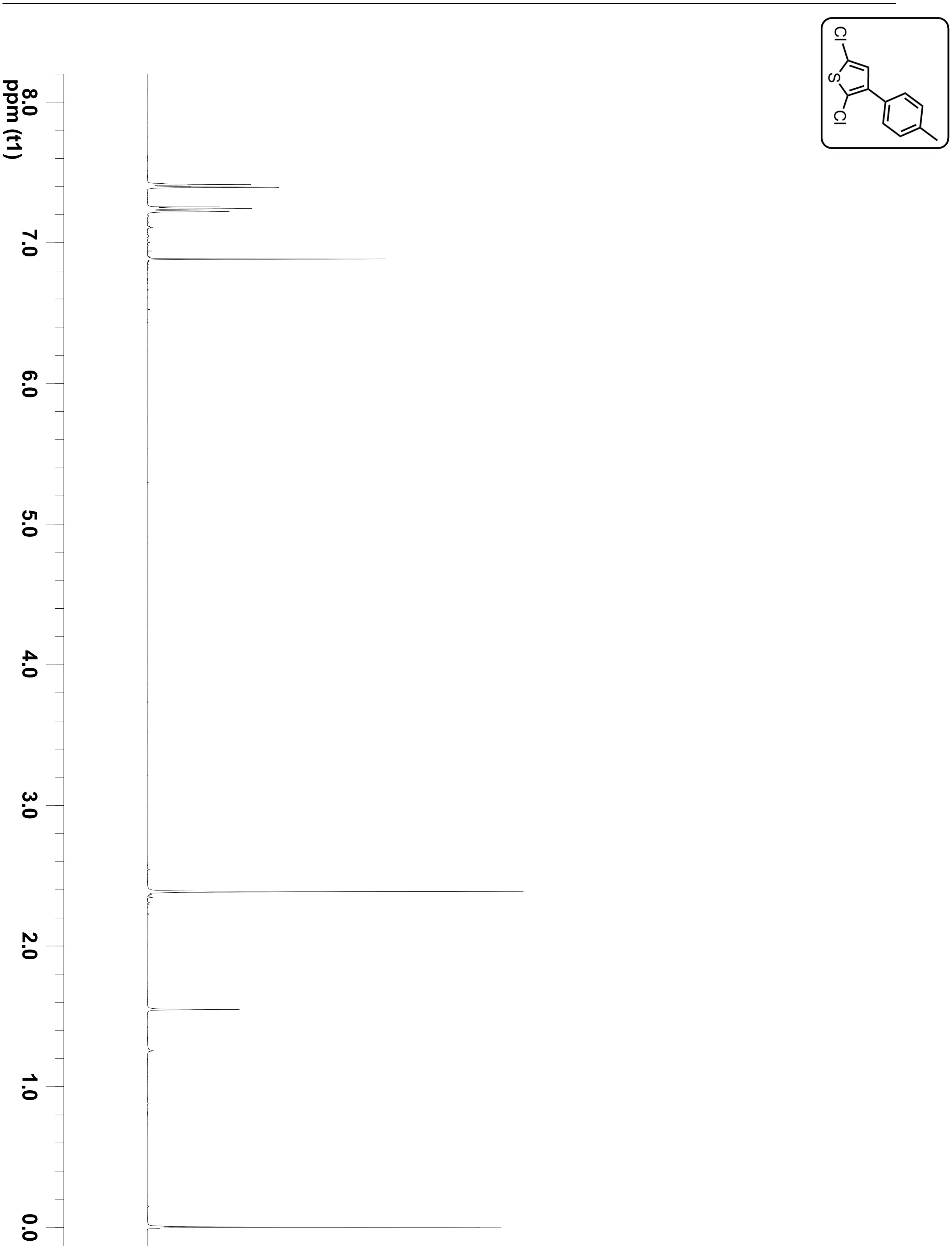
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)
Cl
N
Bn
Cl

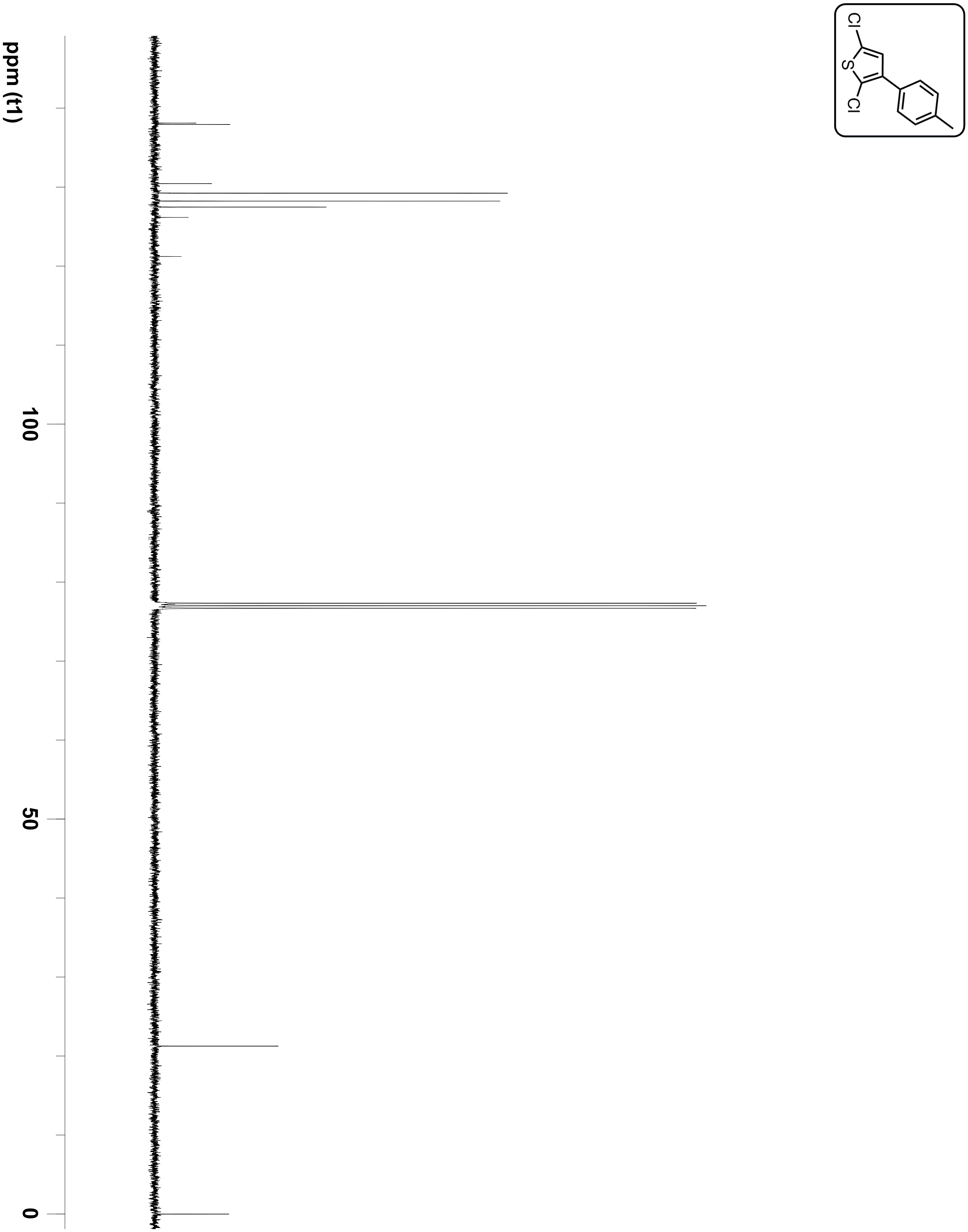

Cl
N
Bn
Cl
ppm (t1)
100
50
0

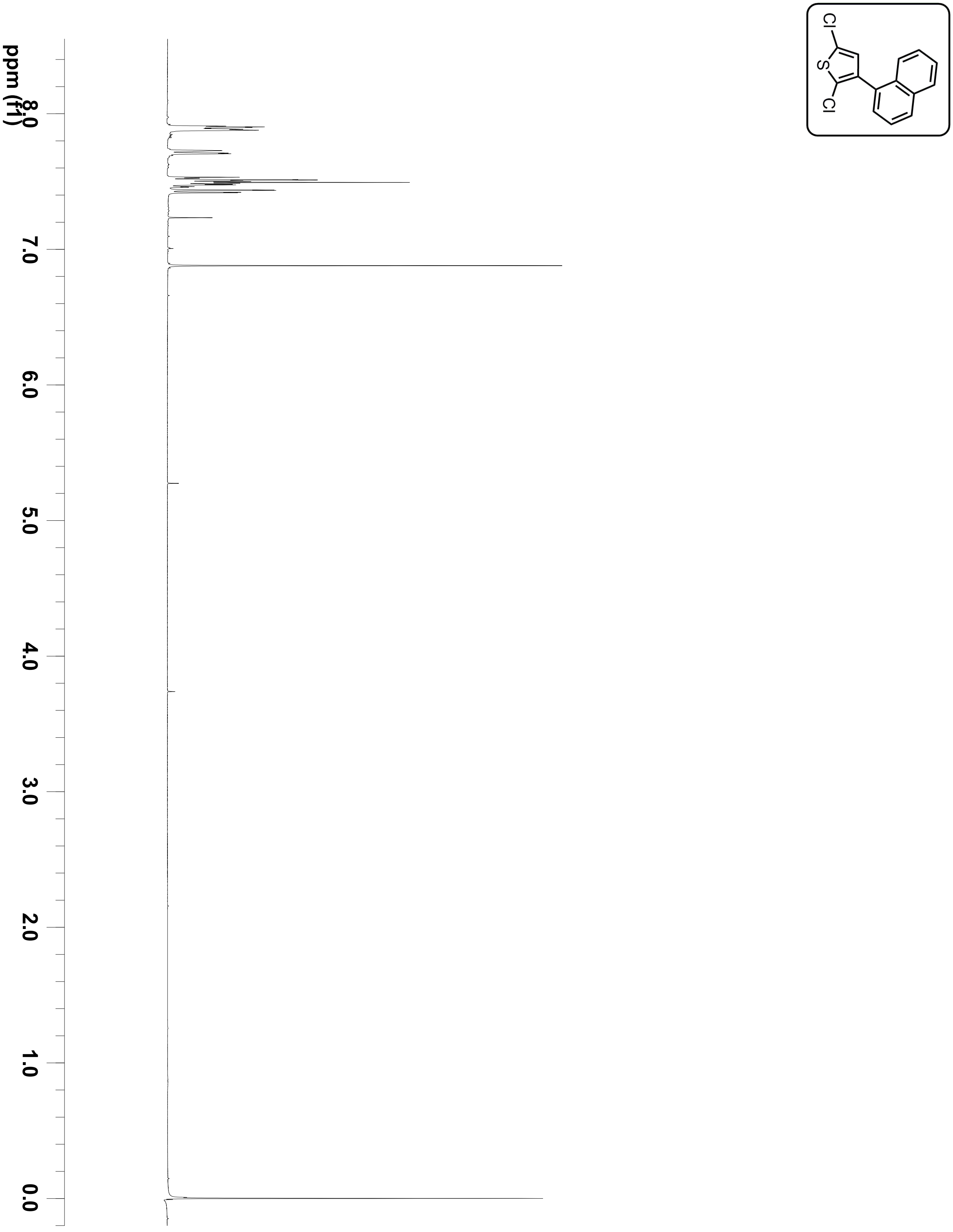

ppm (t1)
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
Cl
N
Bn
Cl
MeO
OMe

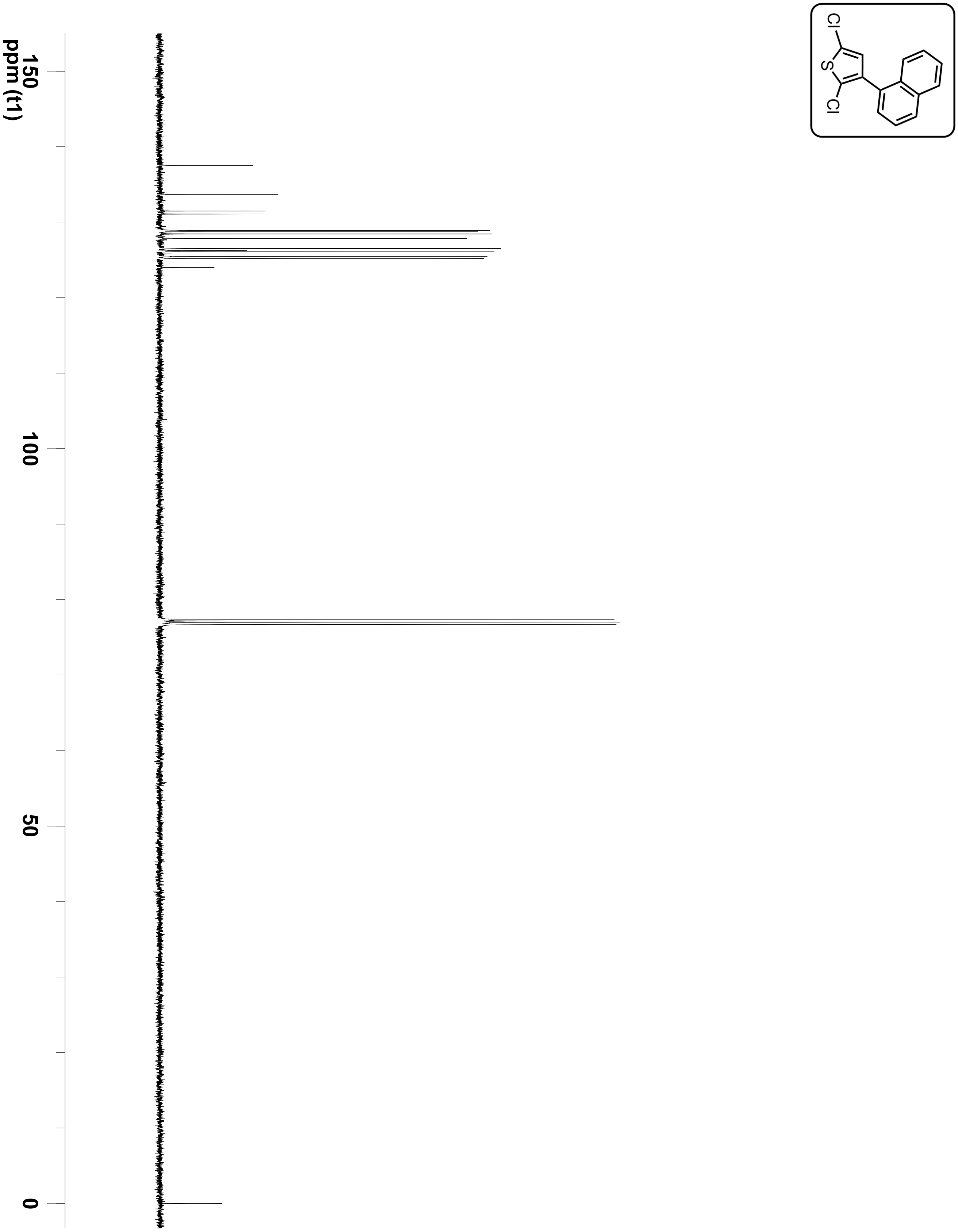


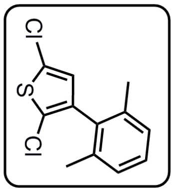
ppm (t1)
150
100
50
0
Cl
N
Bn
Cl
MeO
OMe


Cl
S
Cl
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

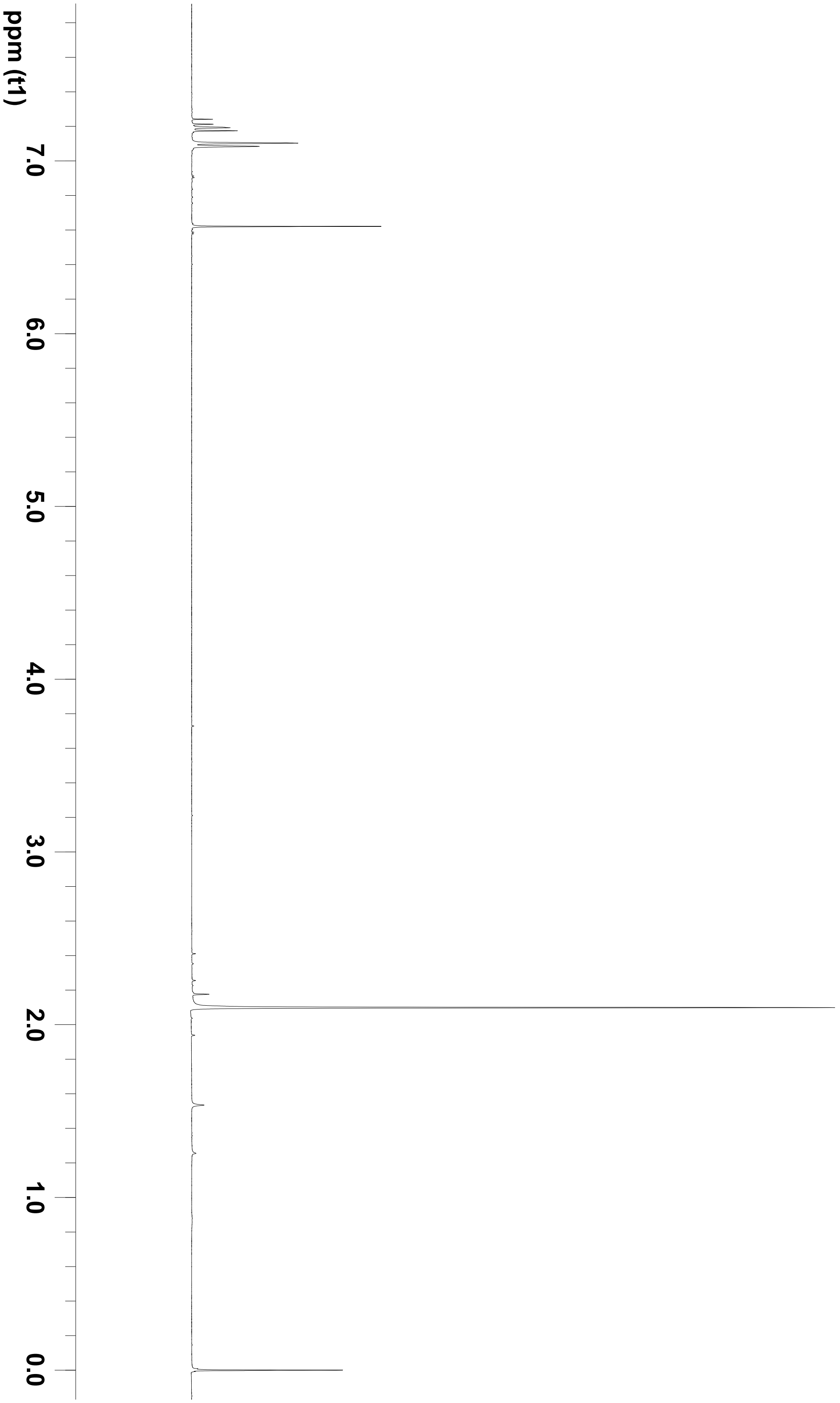

Cl
S
Cl
ppm (t1)
100
50
0


Cl
S
Cl
ppm (f1)
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

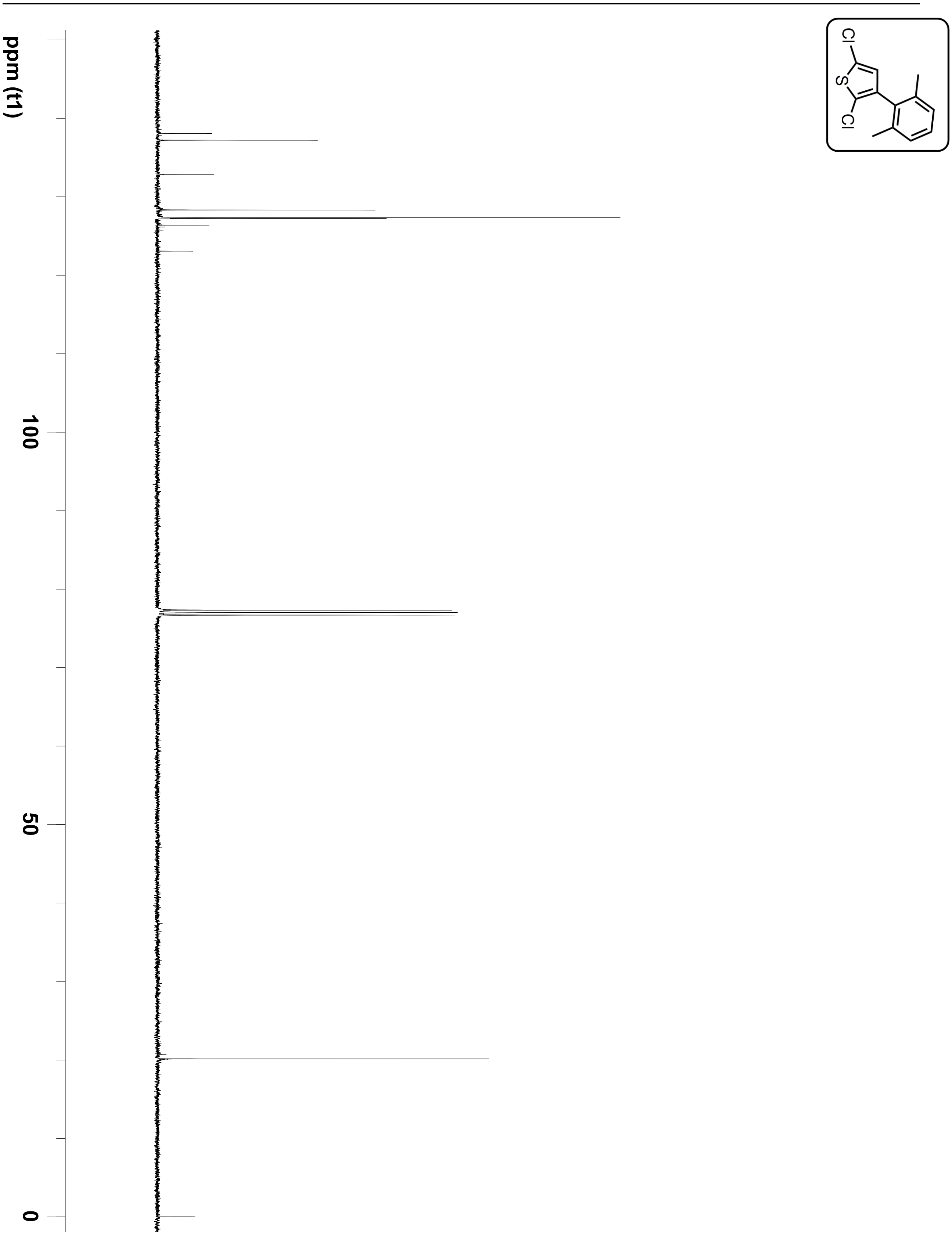

150
100
50
0
ppm (t1)
Cl
S
Cl

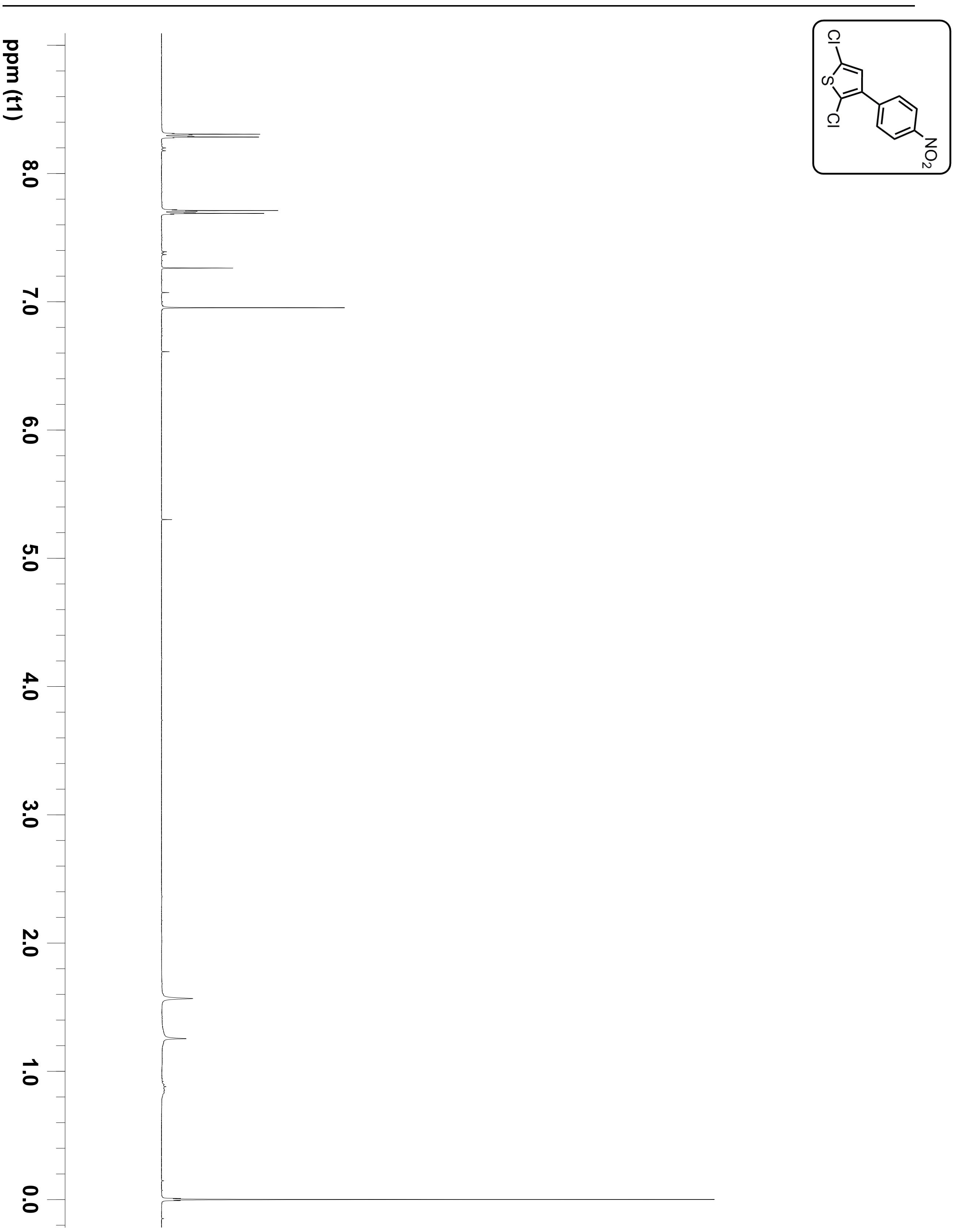


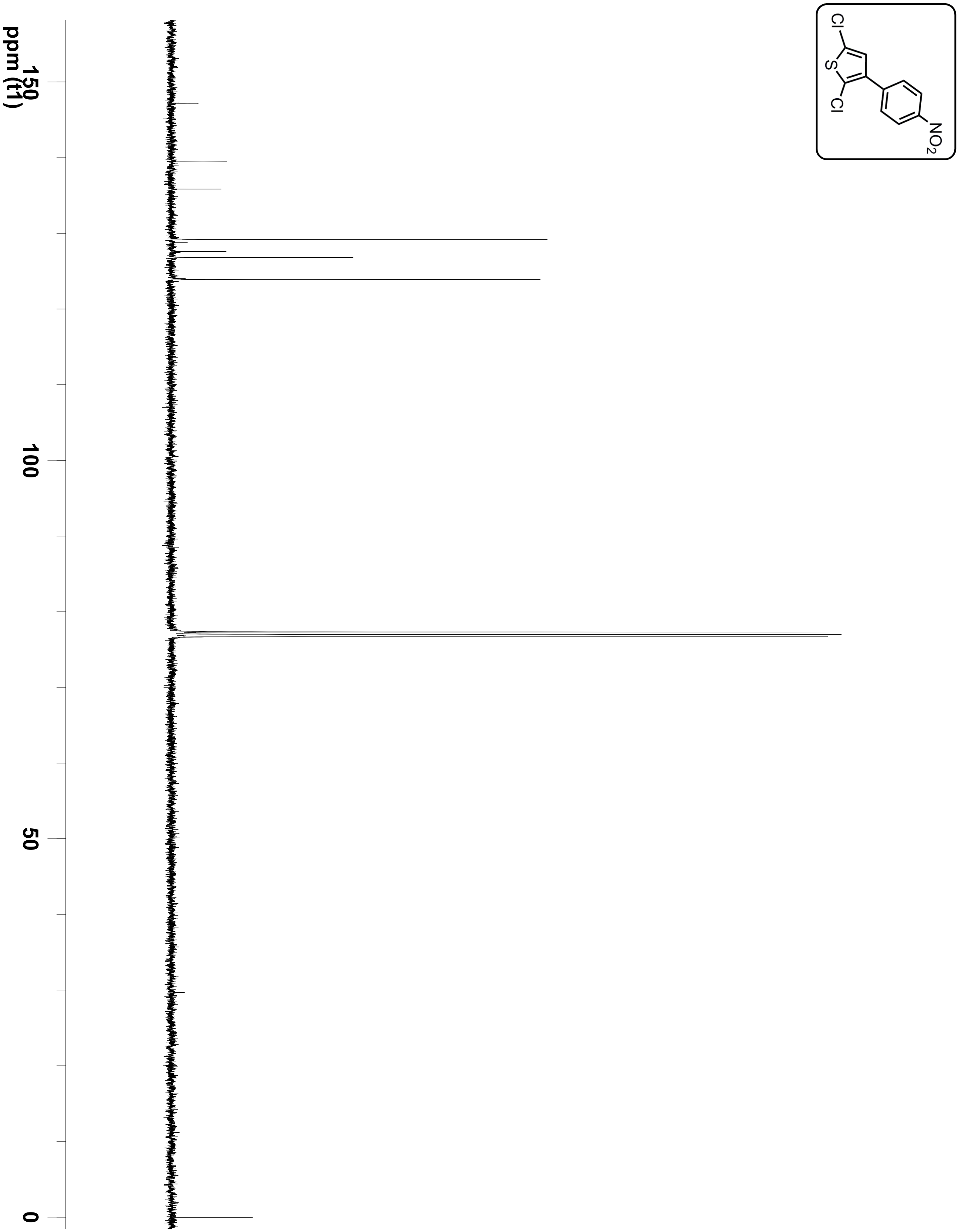
Cl
S
Cl



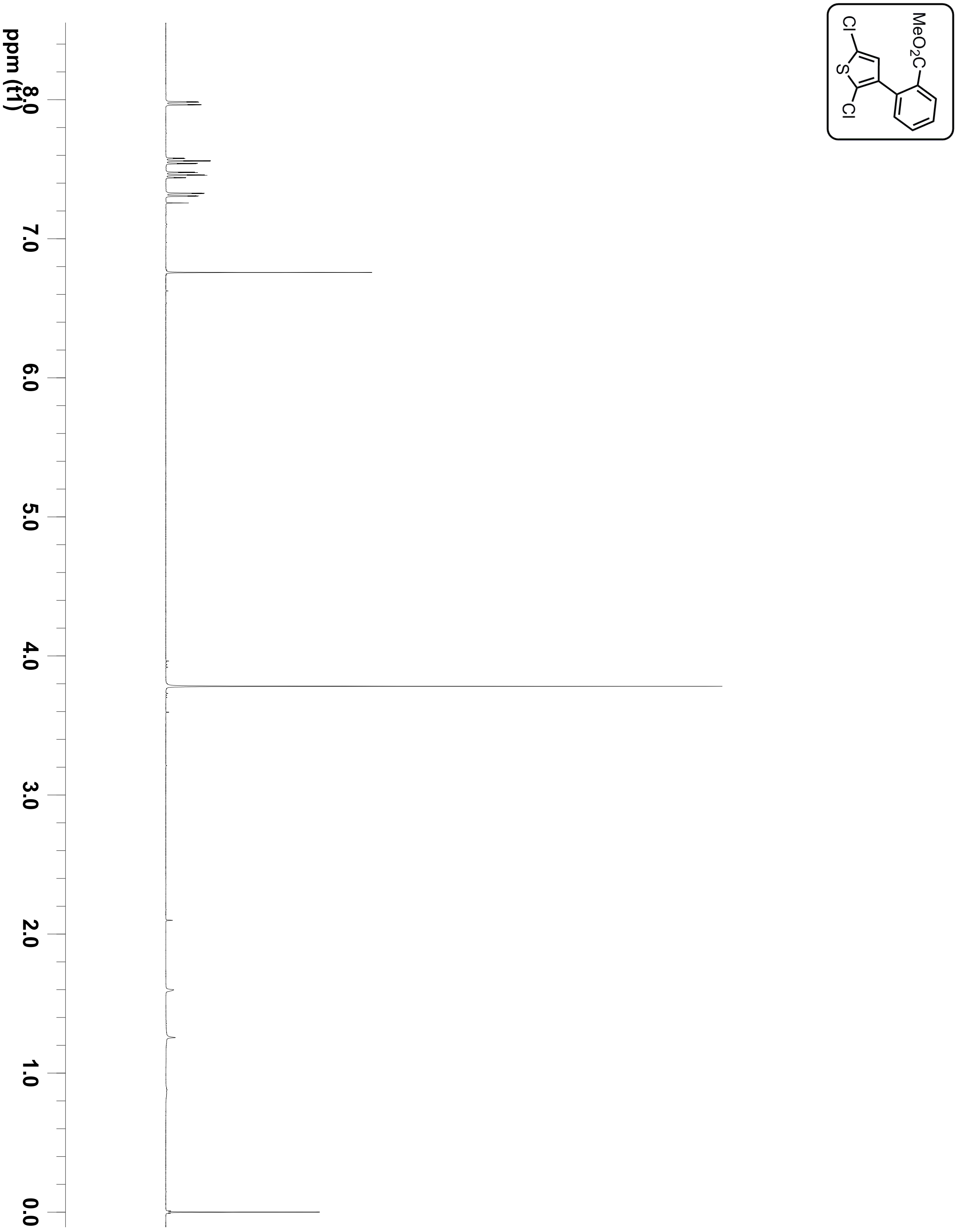
ppm (t1)
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

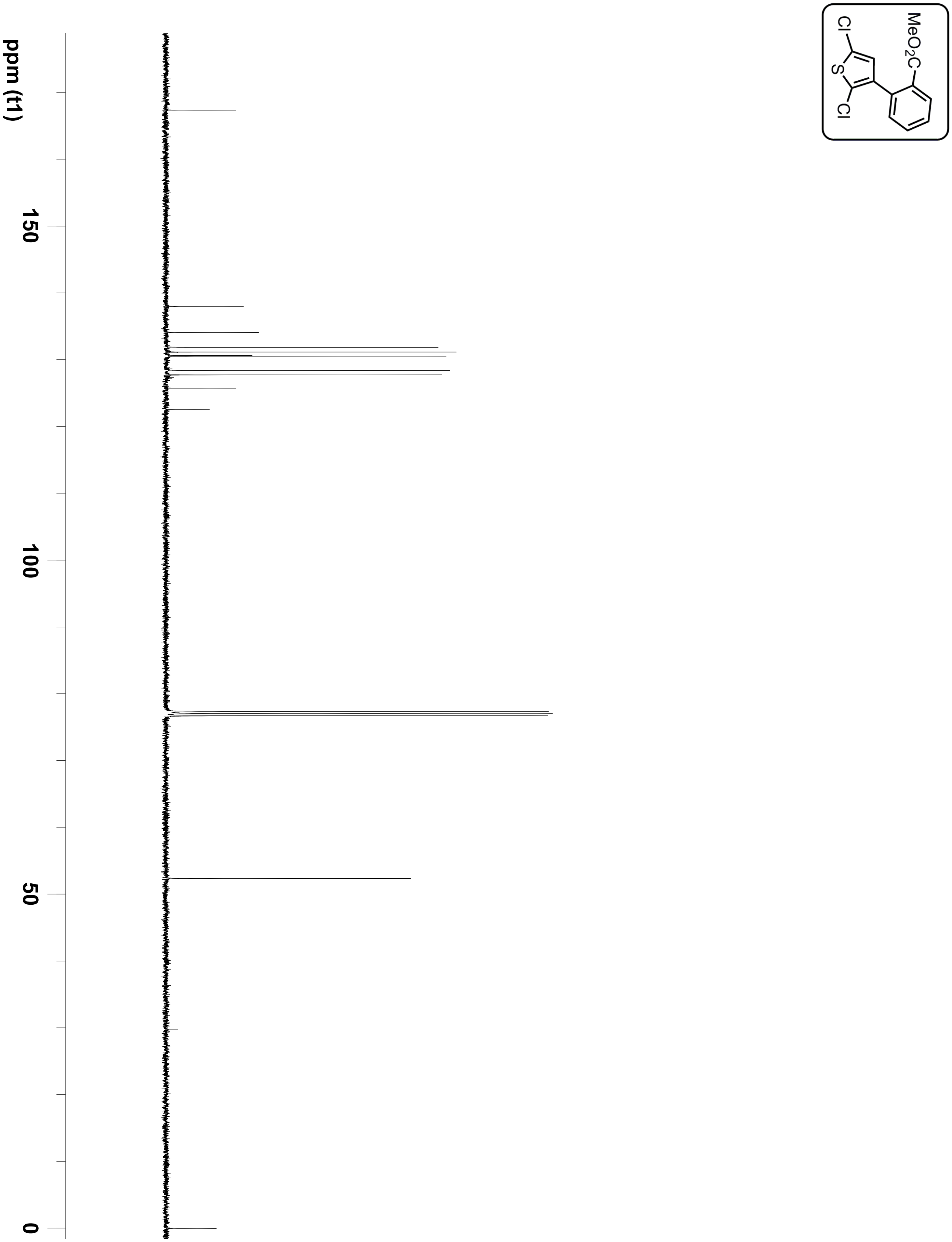

ppm (t1)
100
50
0
Cl
S
Cl

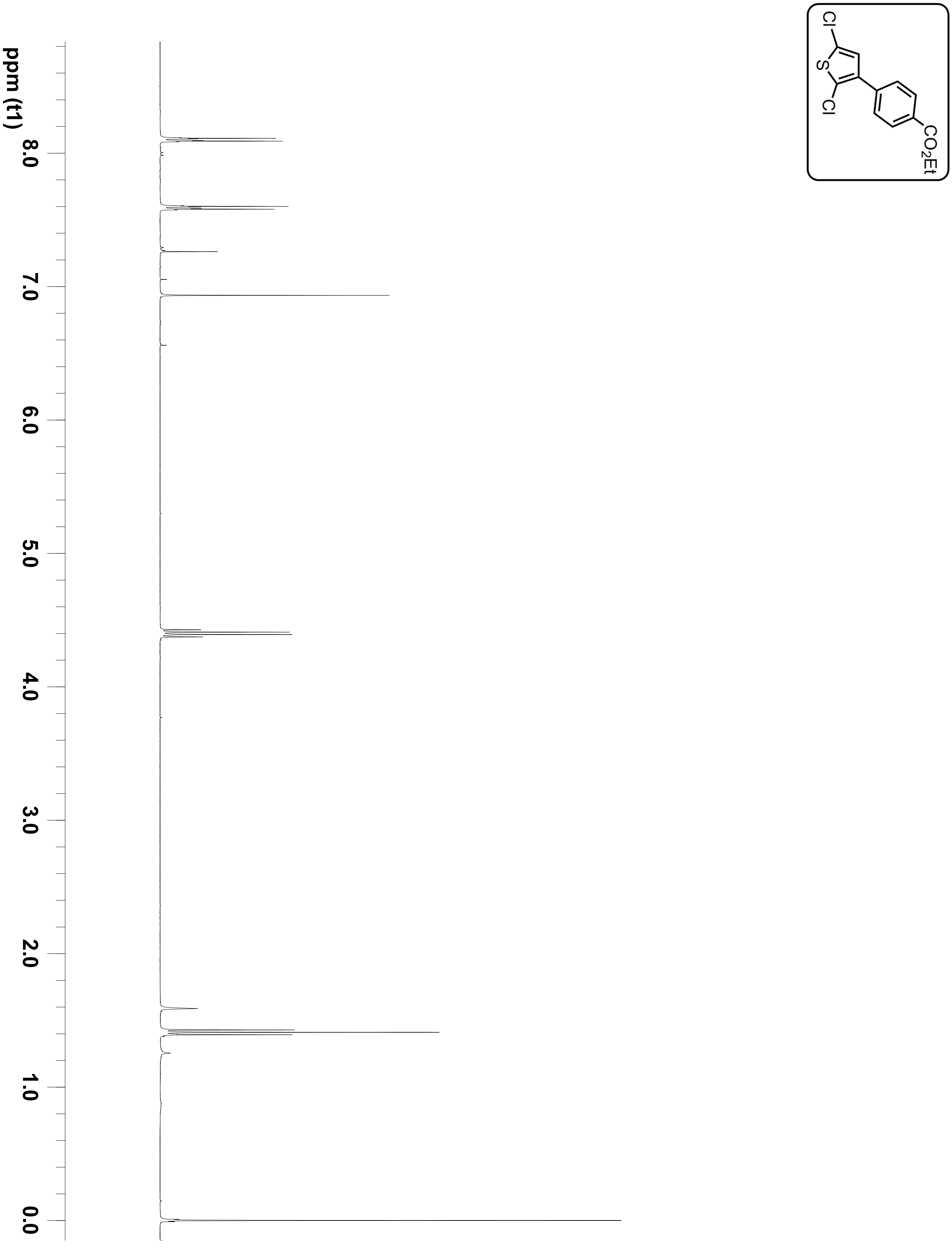

ppm (t1)
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
Cl
S
Cl
NO2

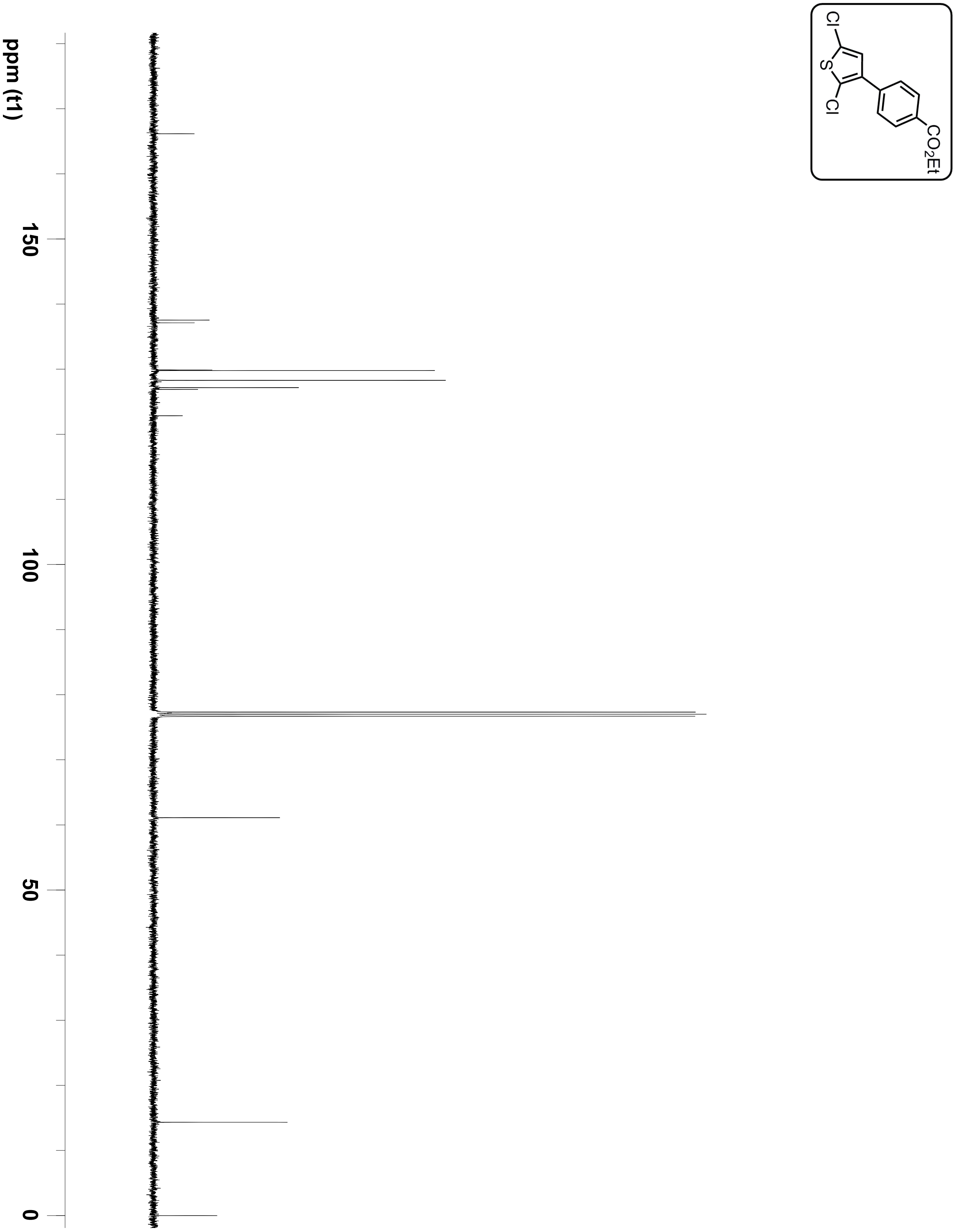


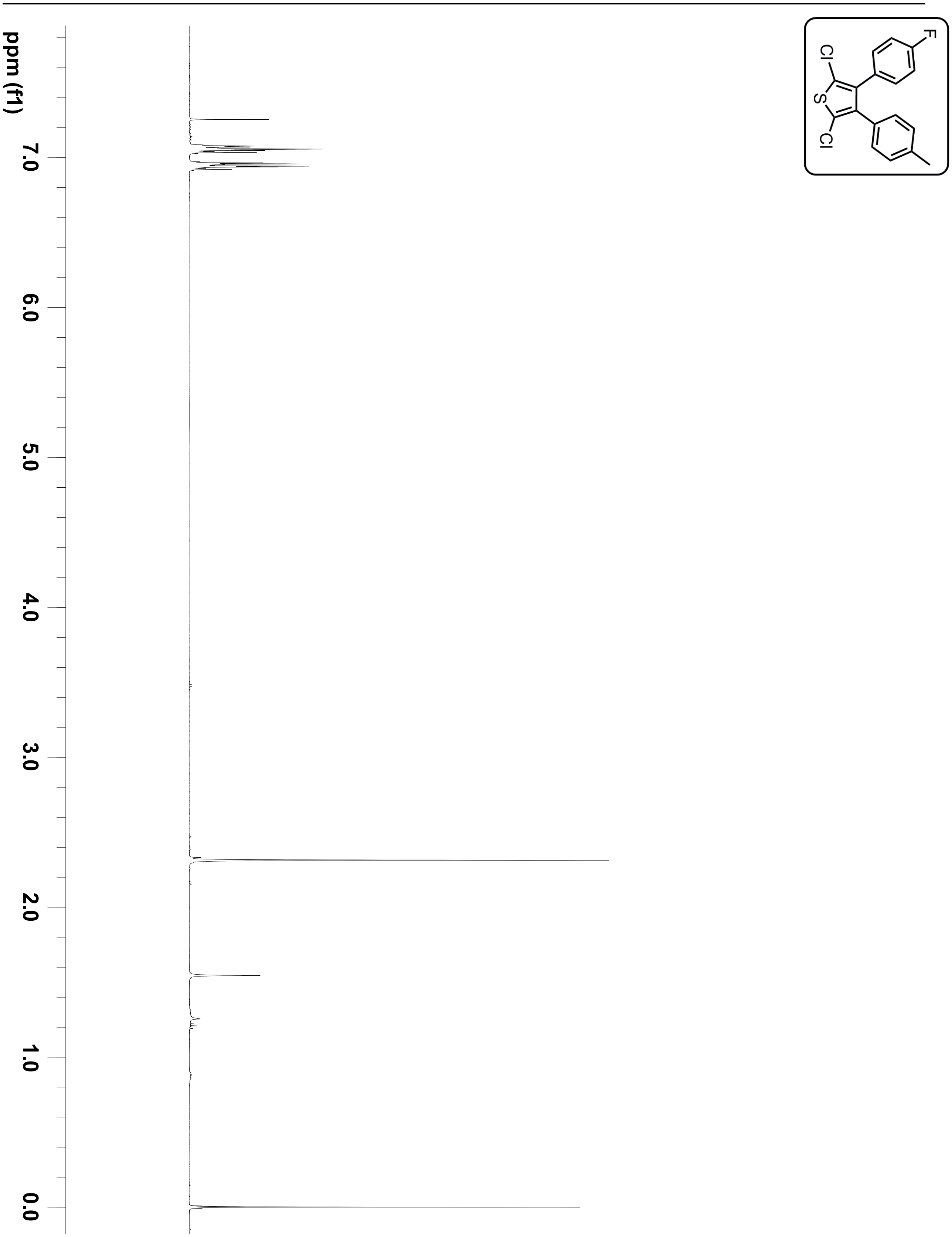
Cl
S
Cl
NO2
150
100
50
0
ppm (t1)

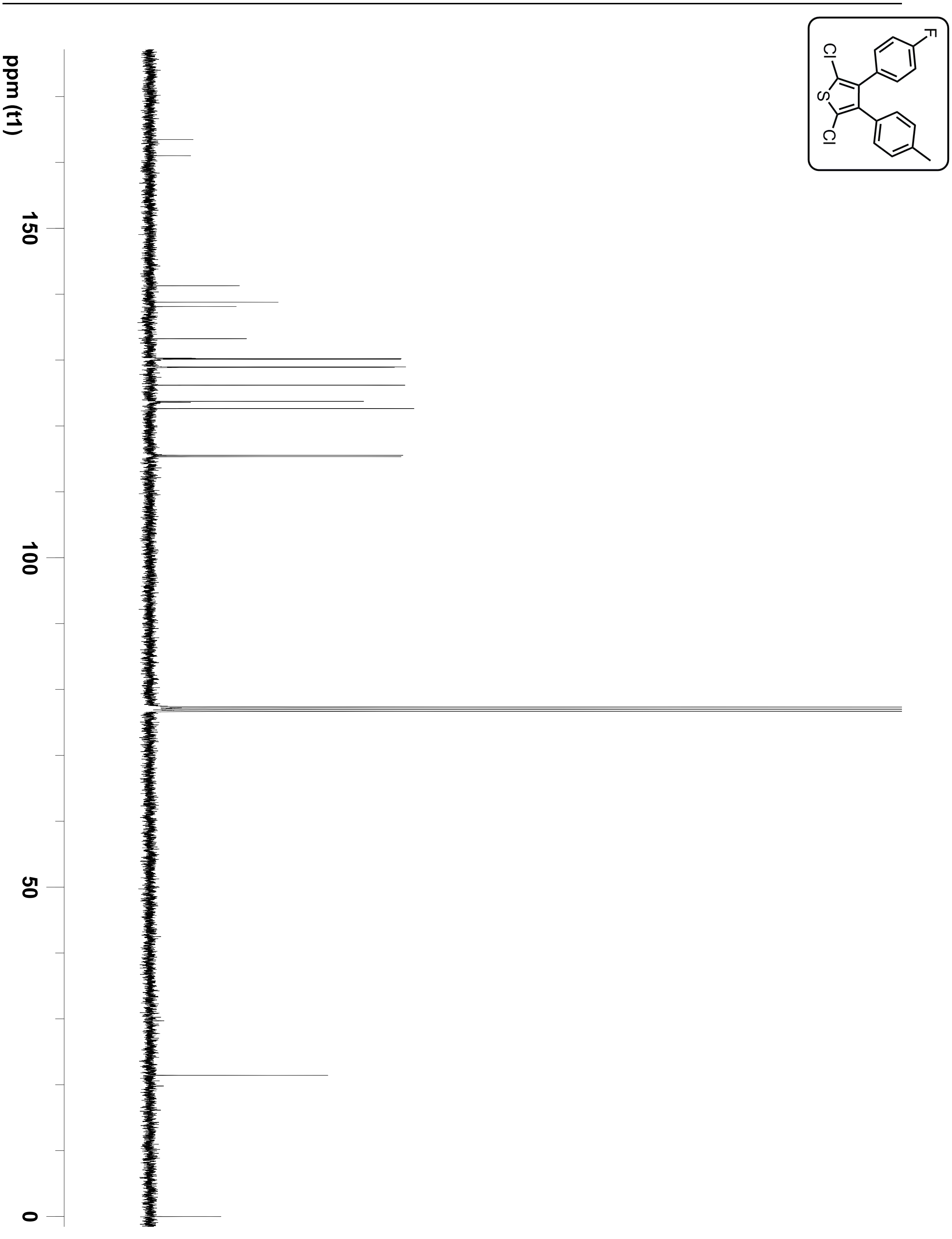

MeO2C
Cl
S
Cl
ppm (t1)
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

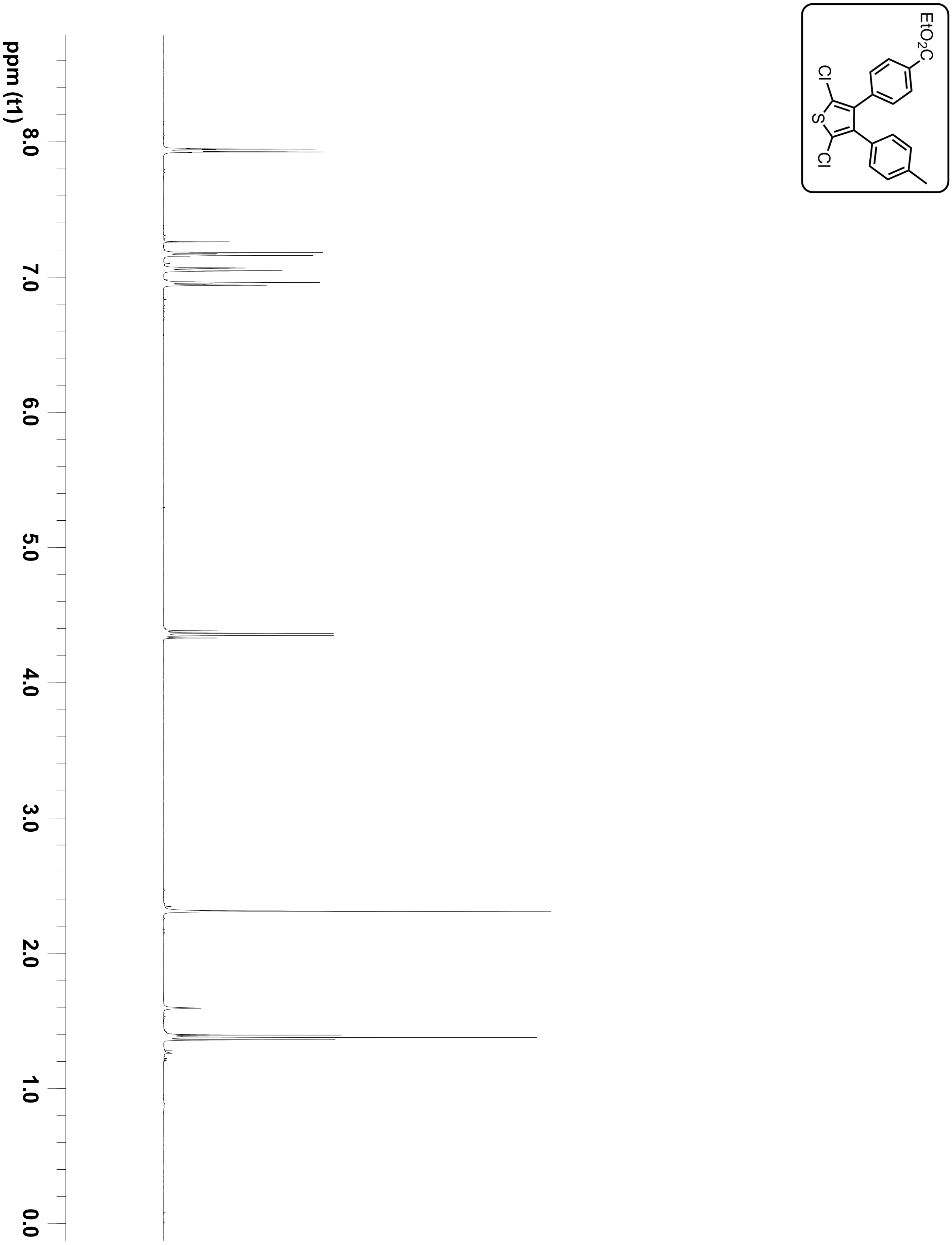

MeO2C
Cl
S
Cl
ppm (t1)
150
100
50
0

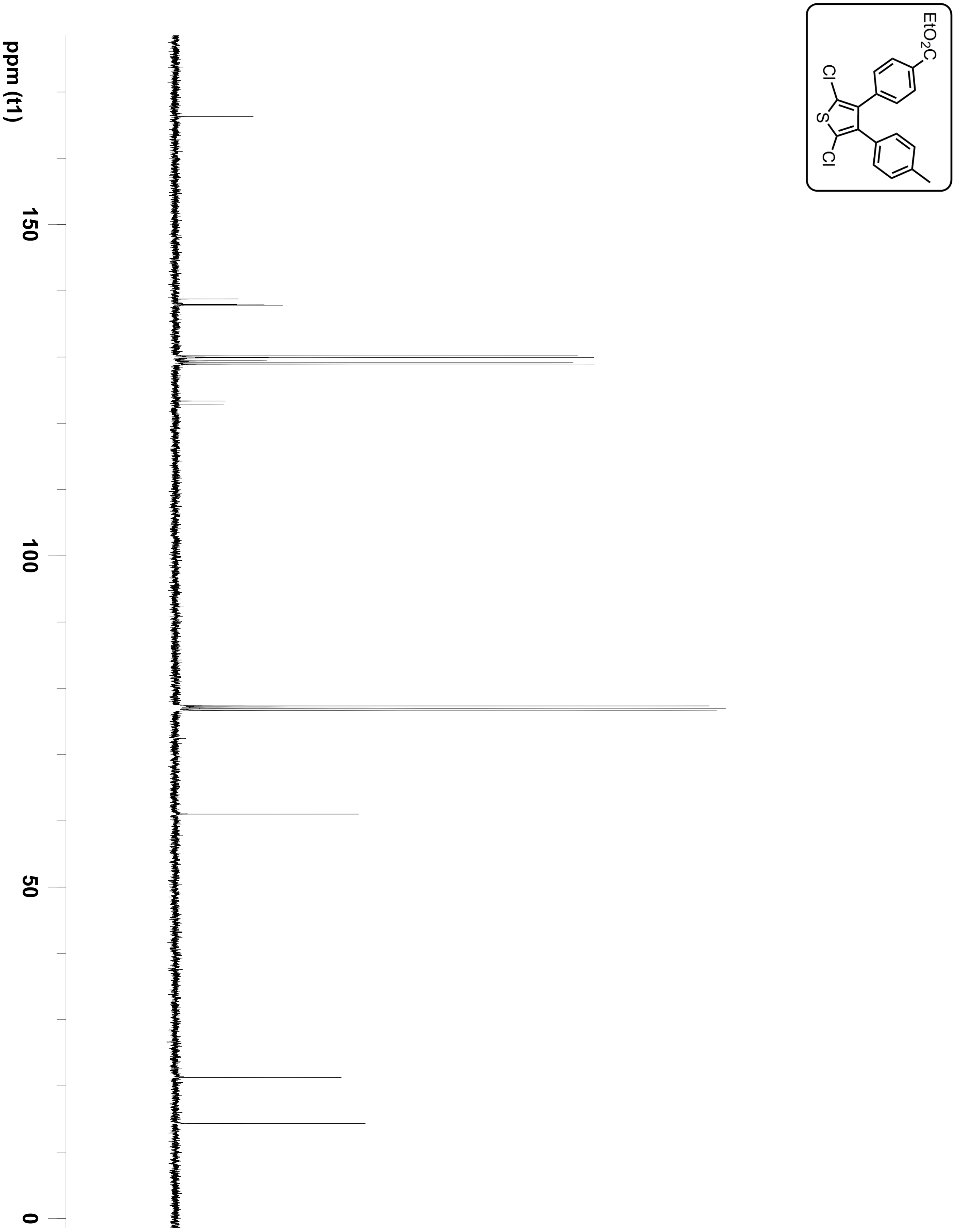

ppm (t1)
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
Cl
S
Cl
CO2Et

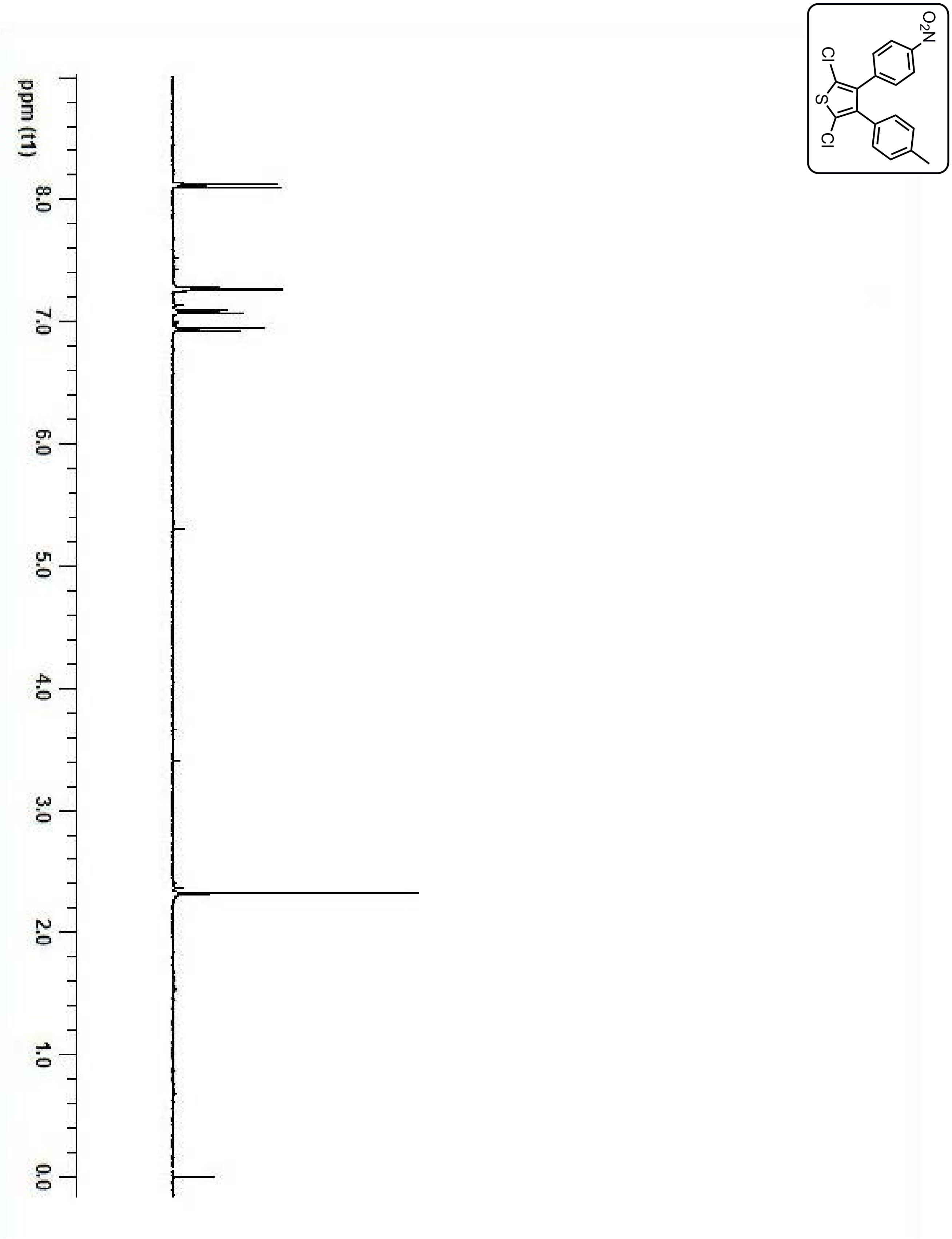

ppm (t1)
150
100
50
0
Cl
S
Cl
CO2Et


ppm (f1)
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
F
Cl
S
Cl

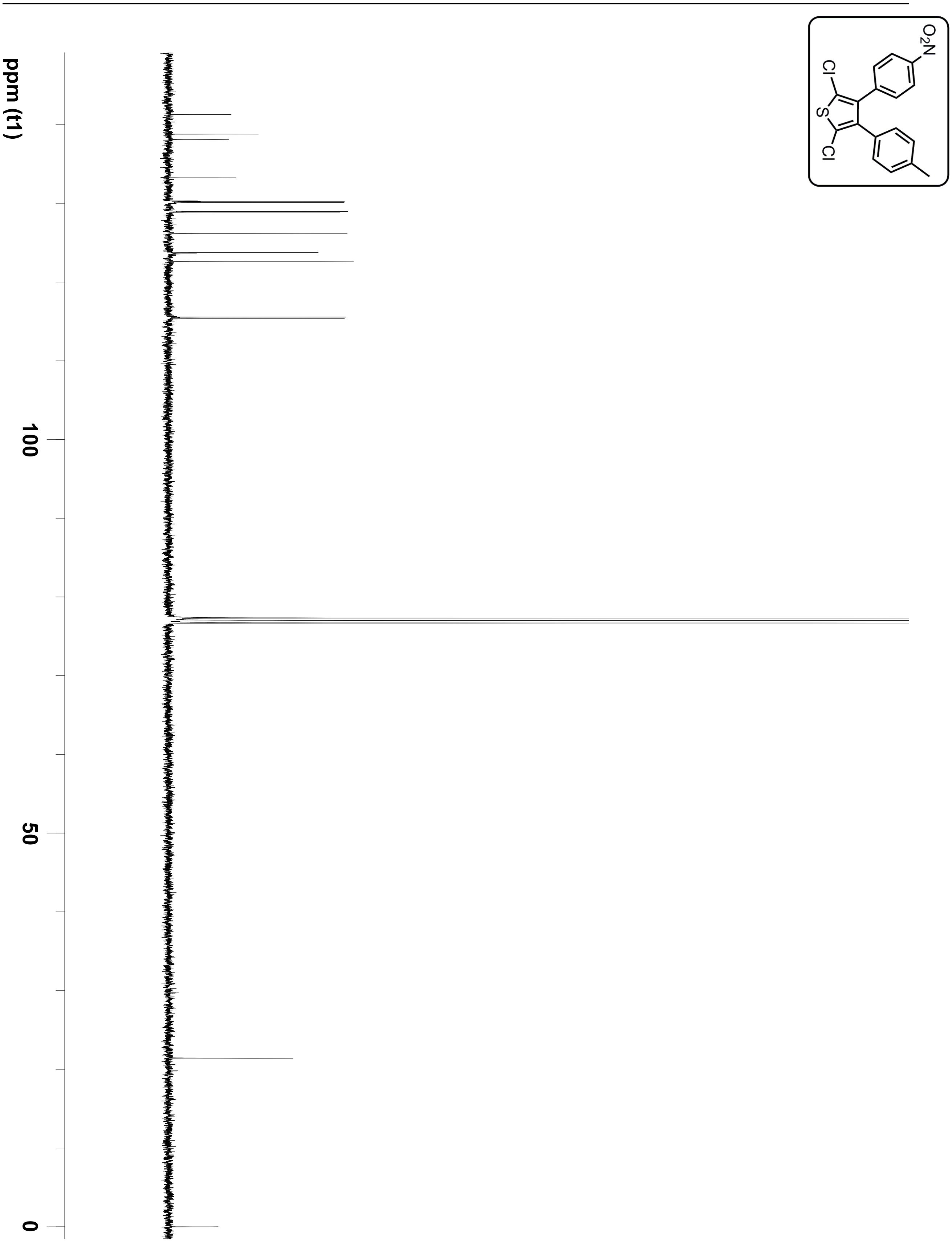

ppm (t1)
150
100
50
0
Cl
S
Cl
F

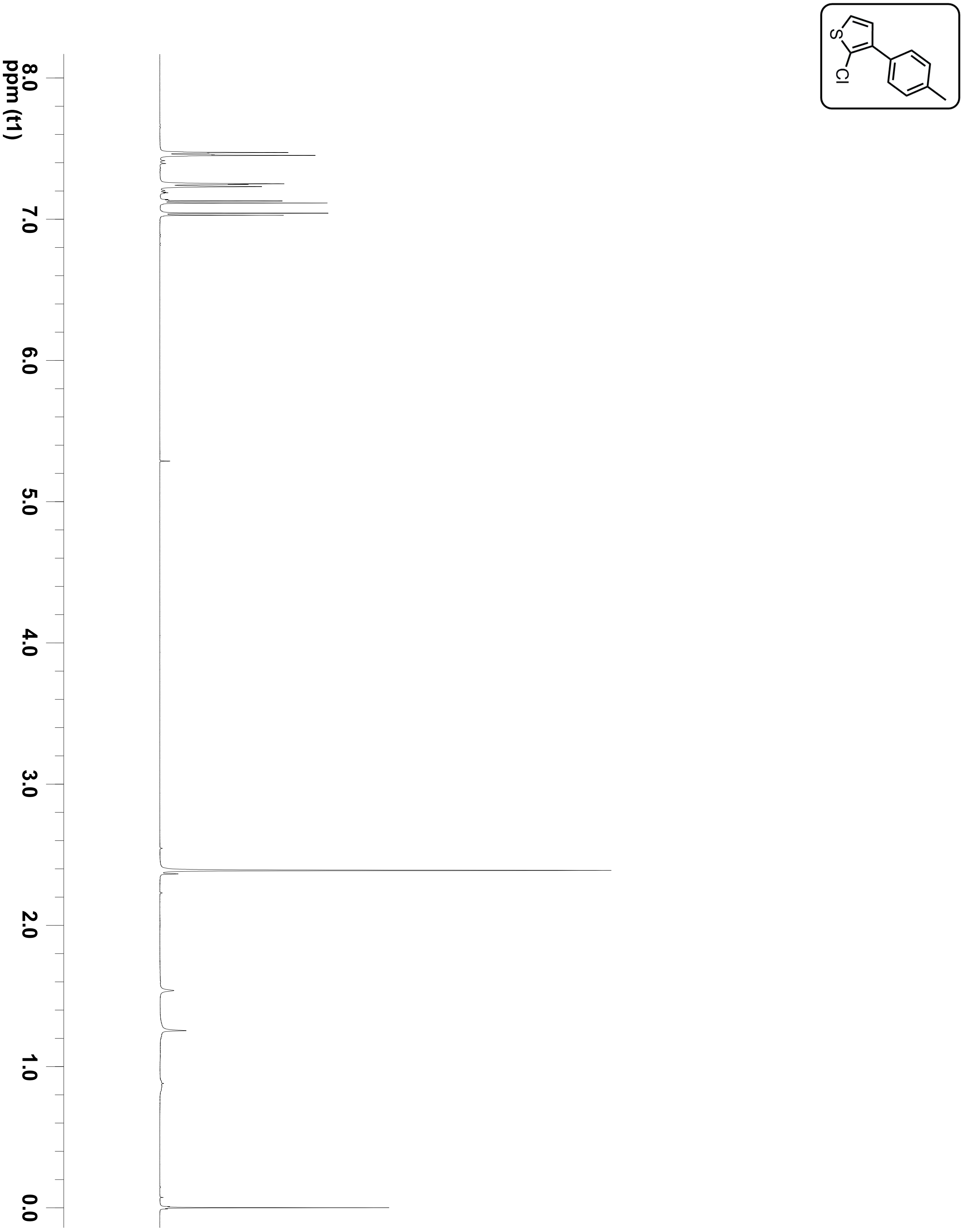

EtO2C
Cl
S
Cl
ppm (t1)
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

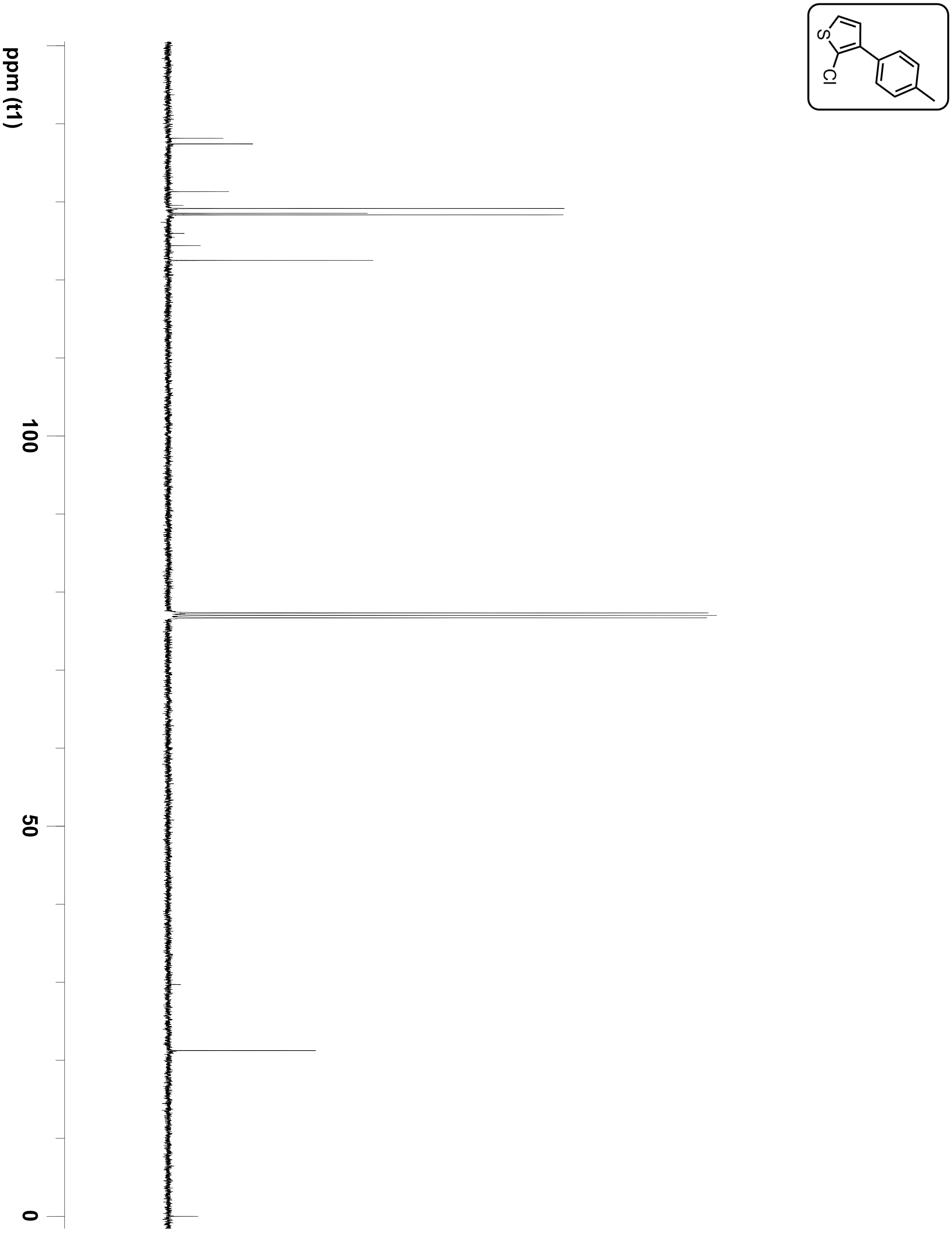

EtO2C
Cl
S
Cl
ppm (t1)
150
100
50
0

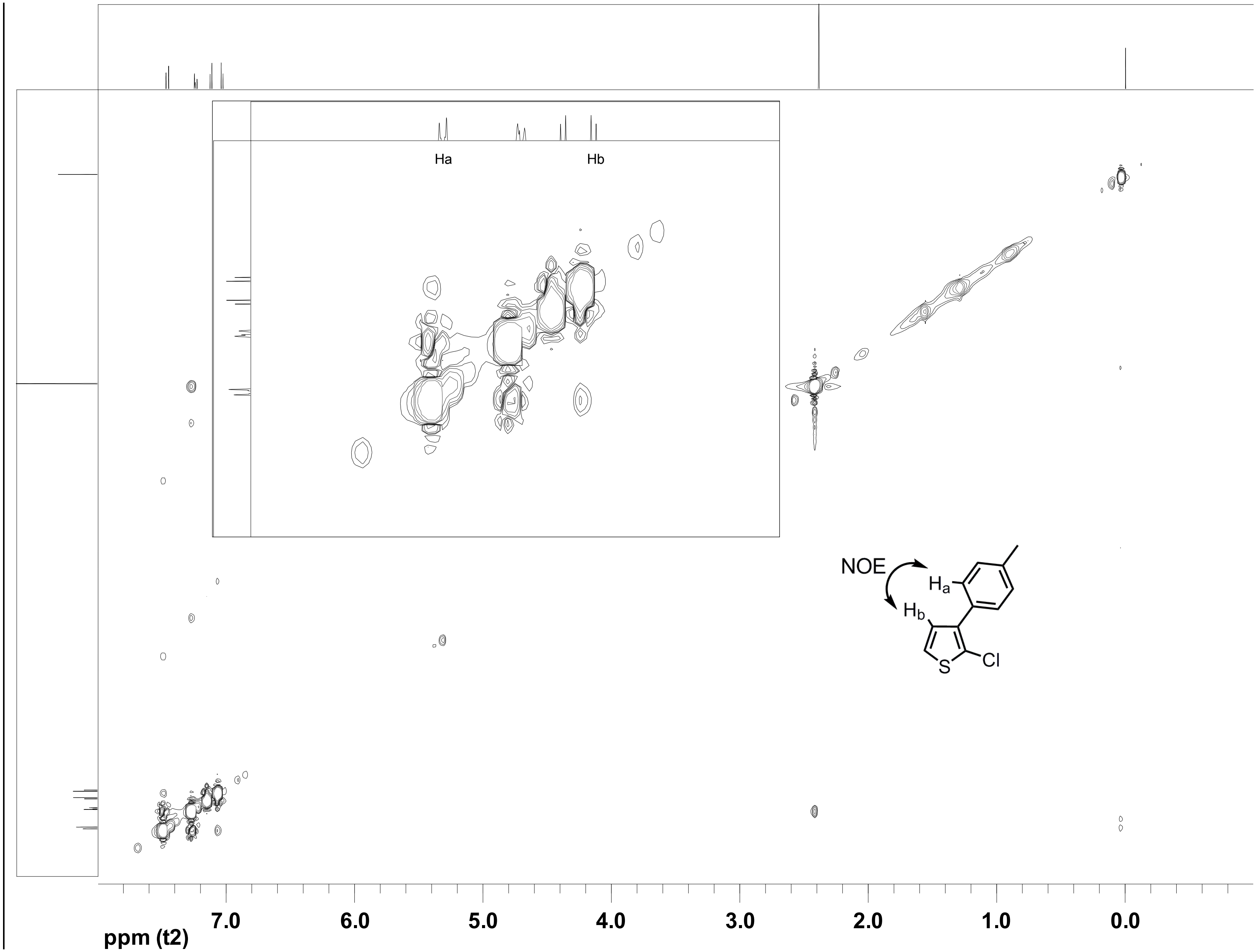


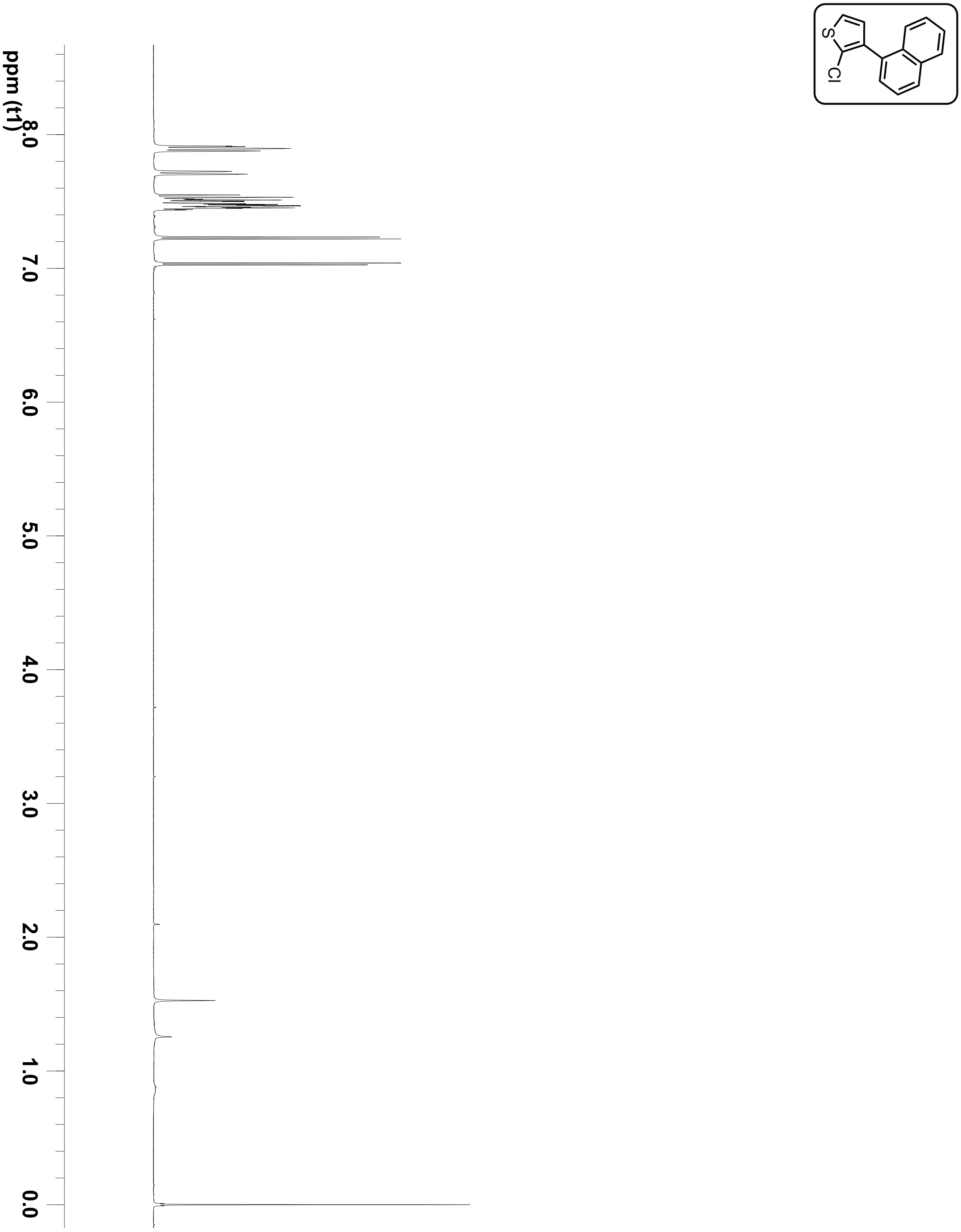
ppm (t1)
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
O2N
Cl
S
Cl

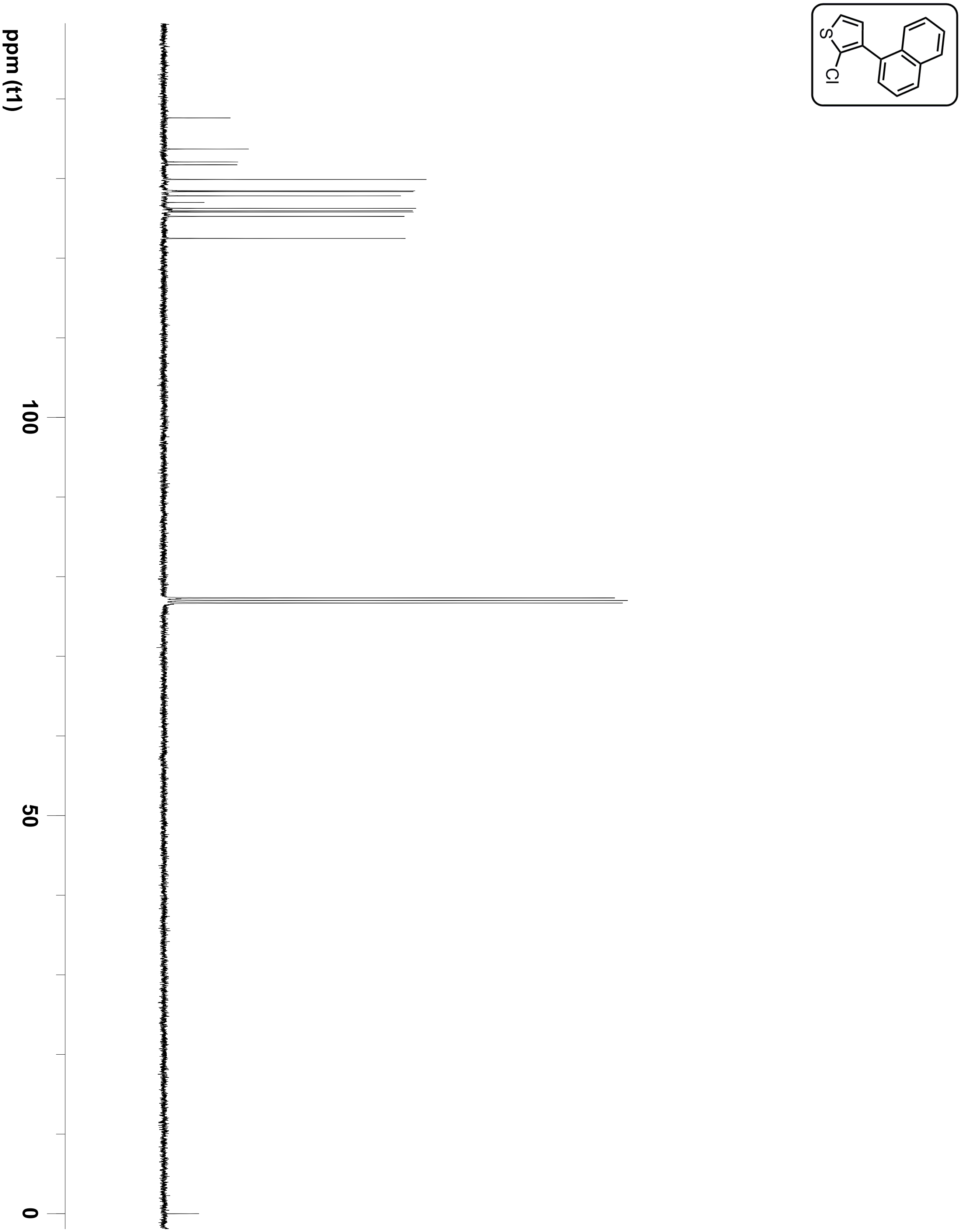

O2N
Cl
S
Cl
ppm (t1)
100
50
0

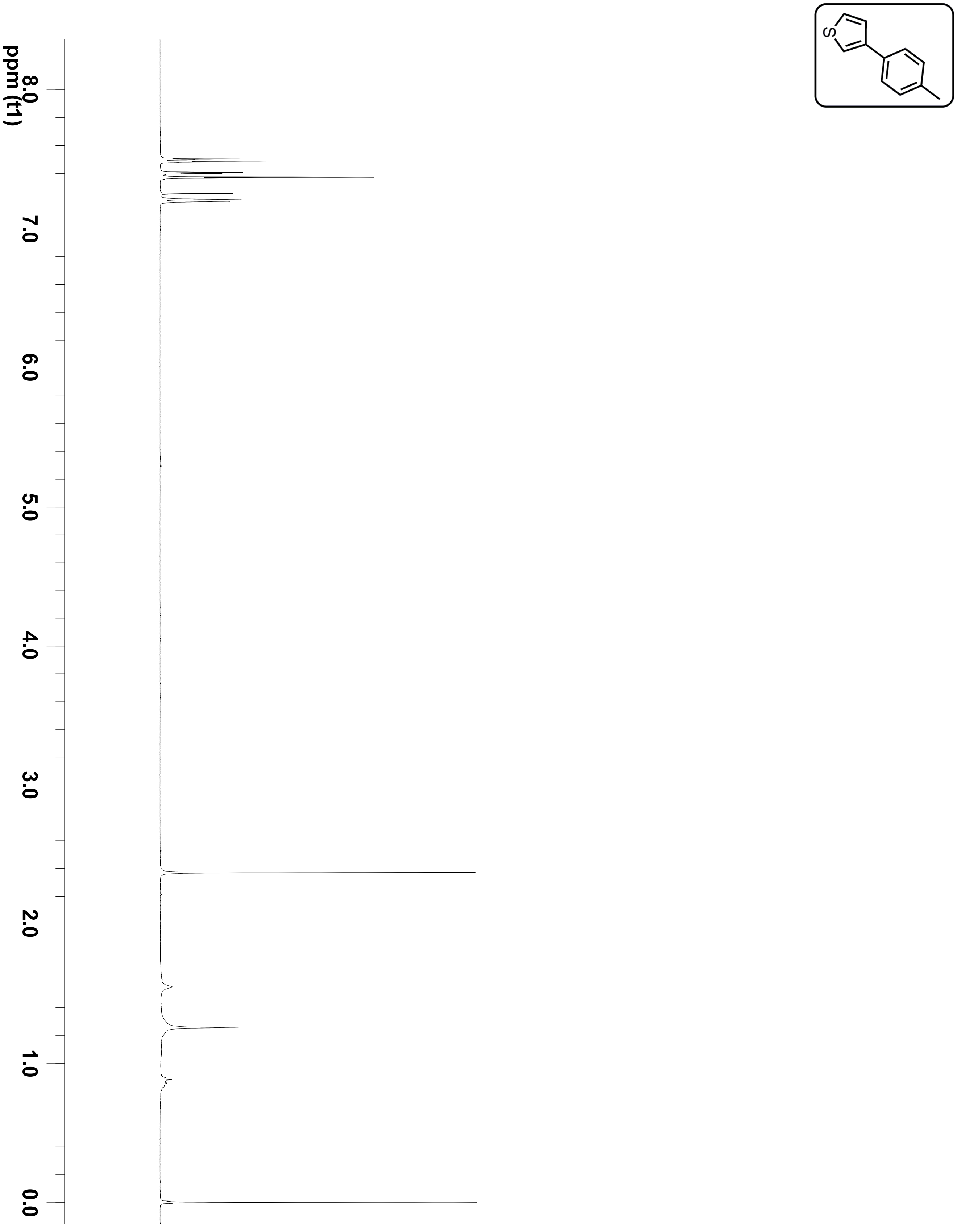

S
Cl
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

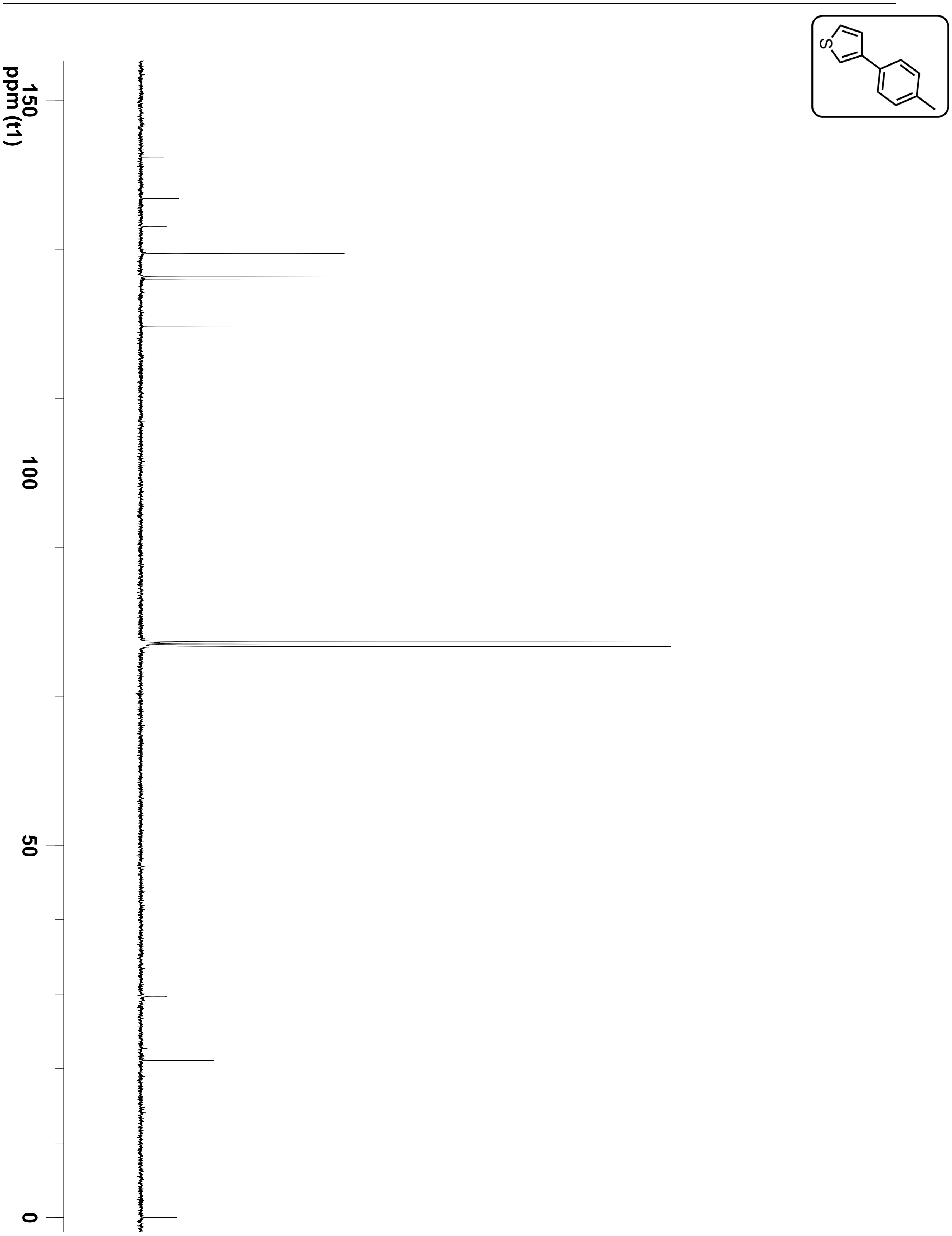

ppm (t1)
100
50
0
S
Cl

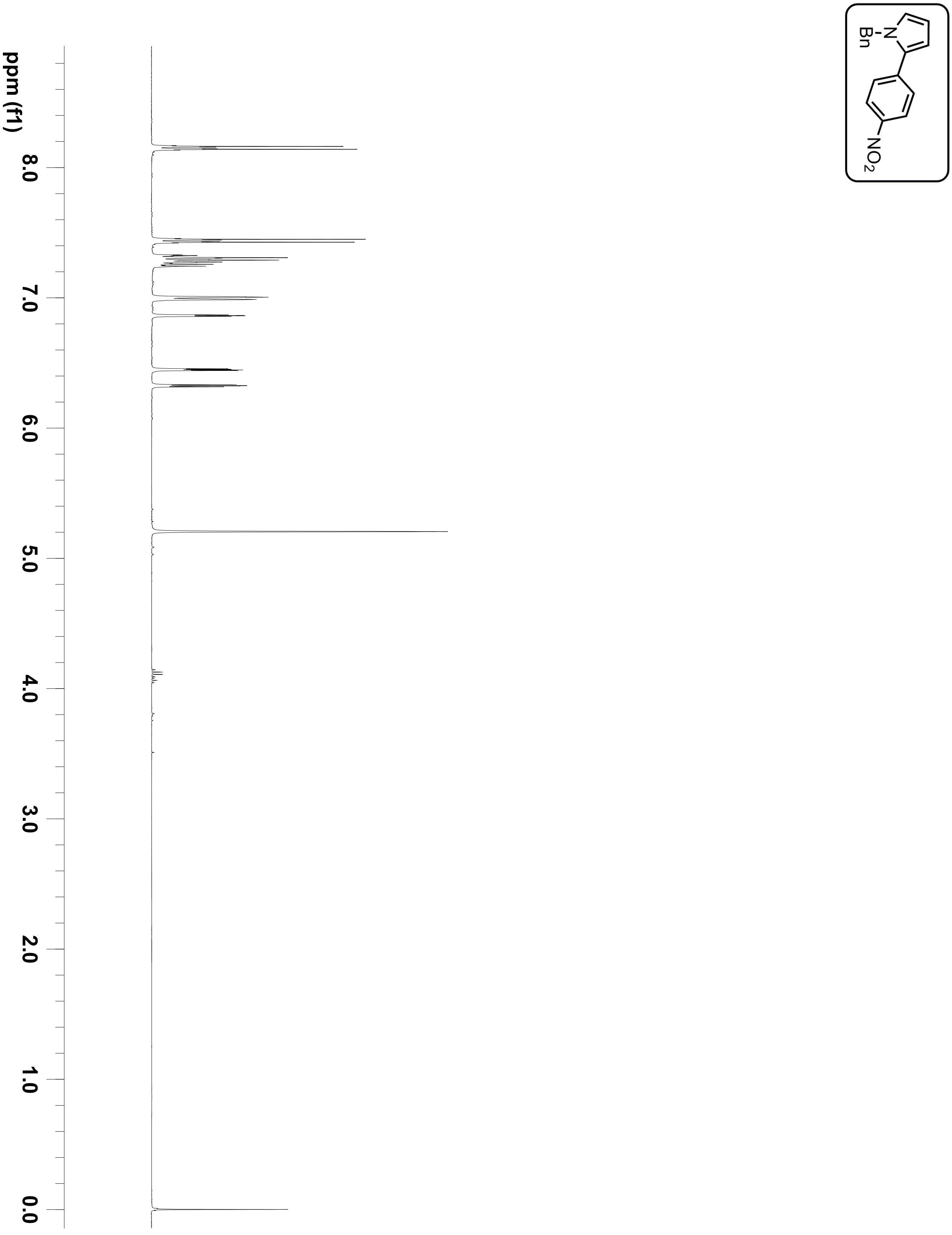

Ha
Hb
NOE
H_a
H_b
S
Cl
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t2)

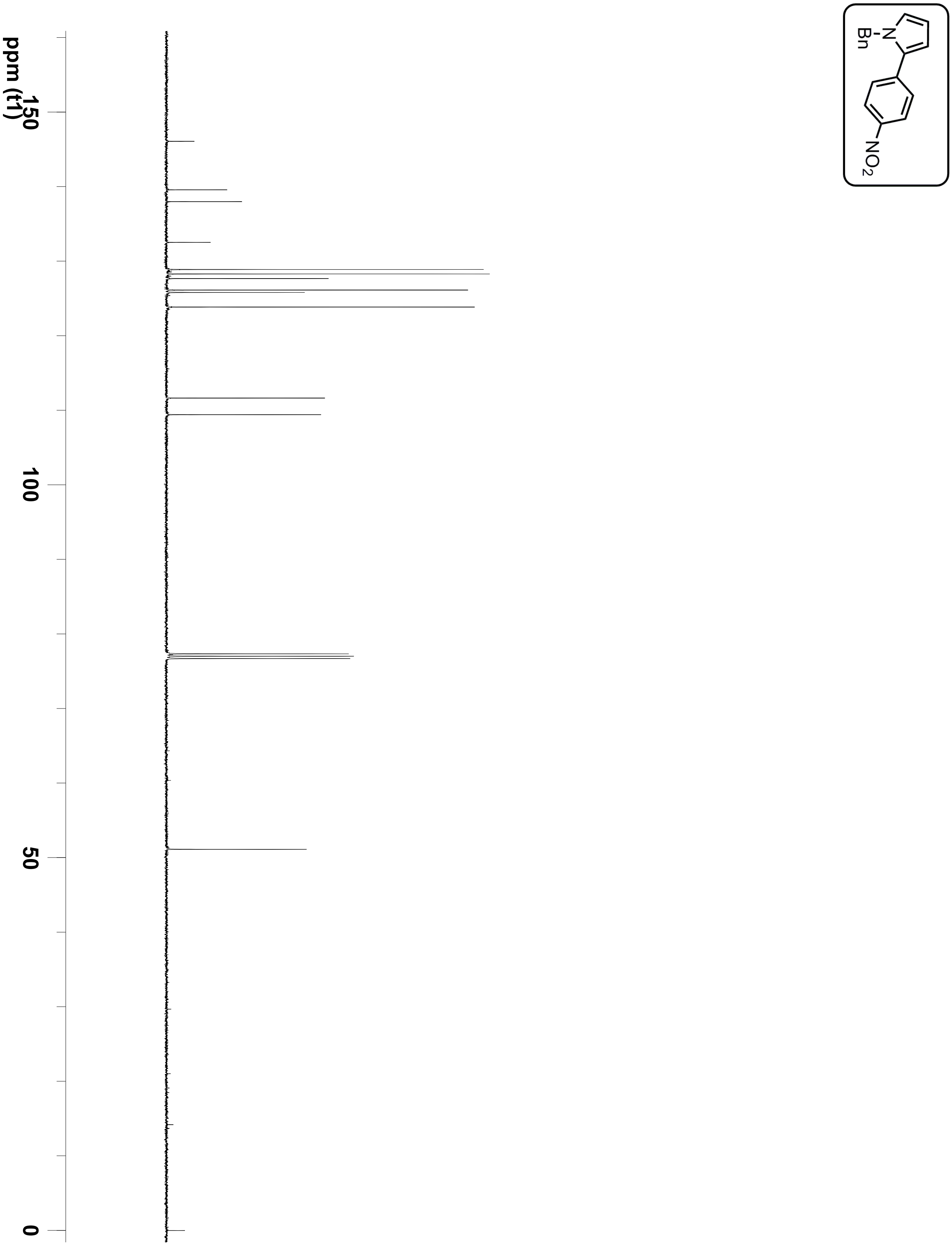

S
Cl
ppm (t1)
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0


ppm (t1)
100
50
0
S
Cl

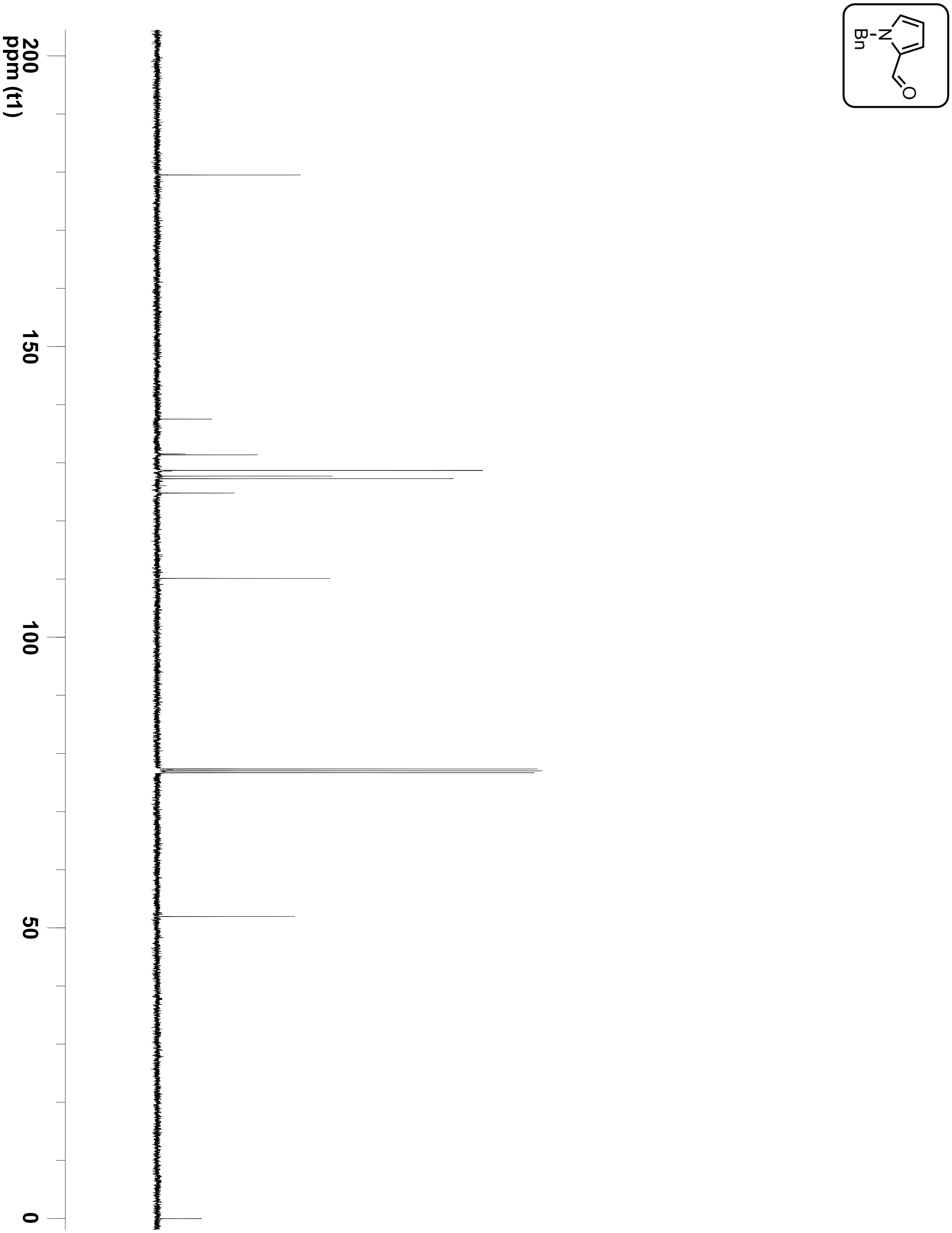

S
ppm (t1)
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

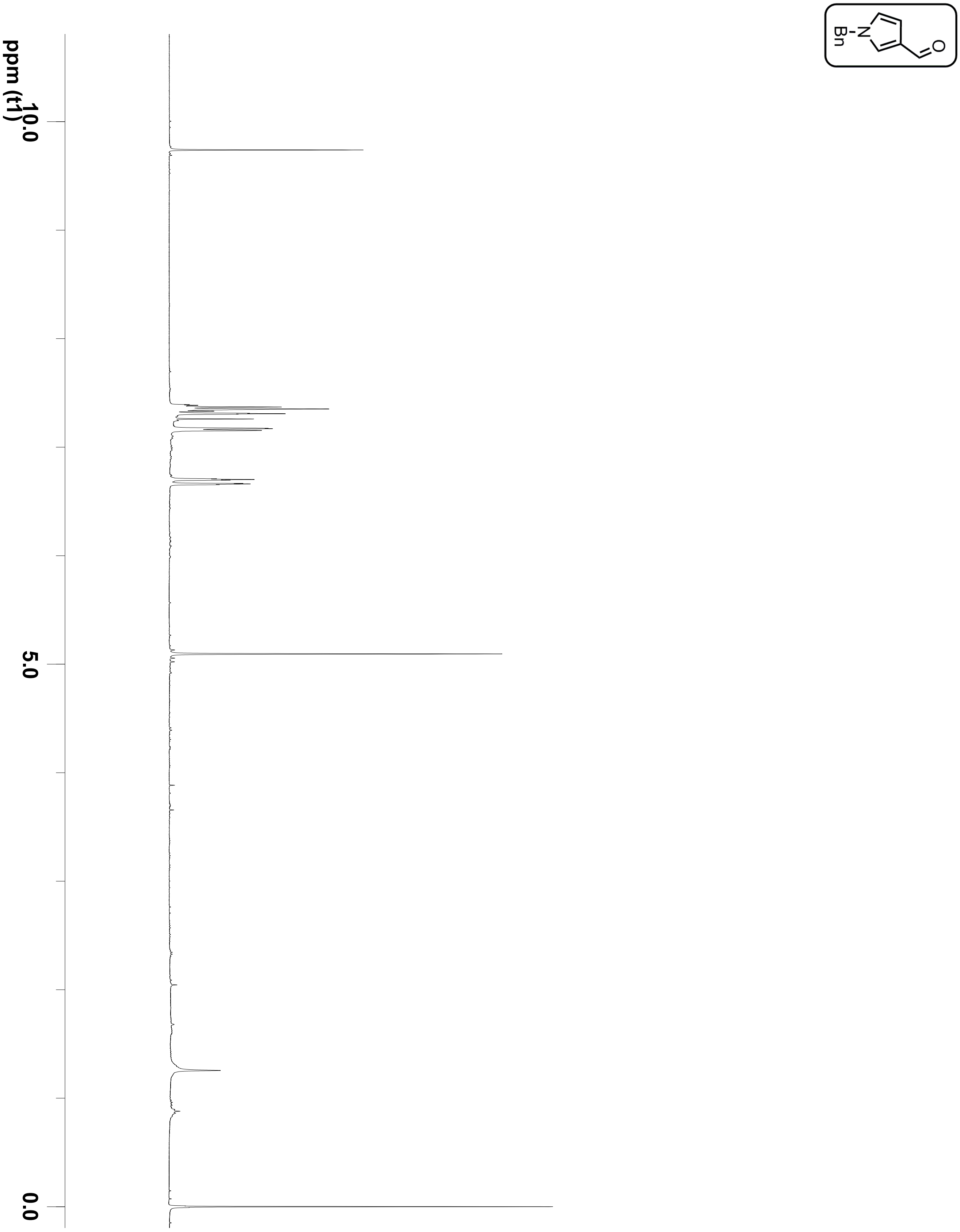

S
150
ppm (t1)
100
50
0

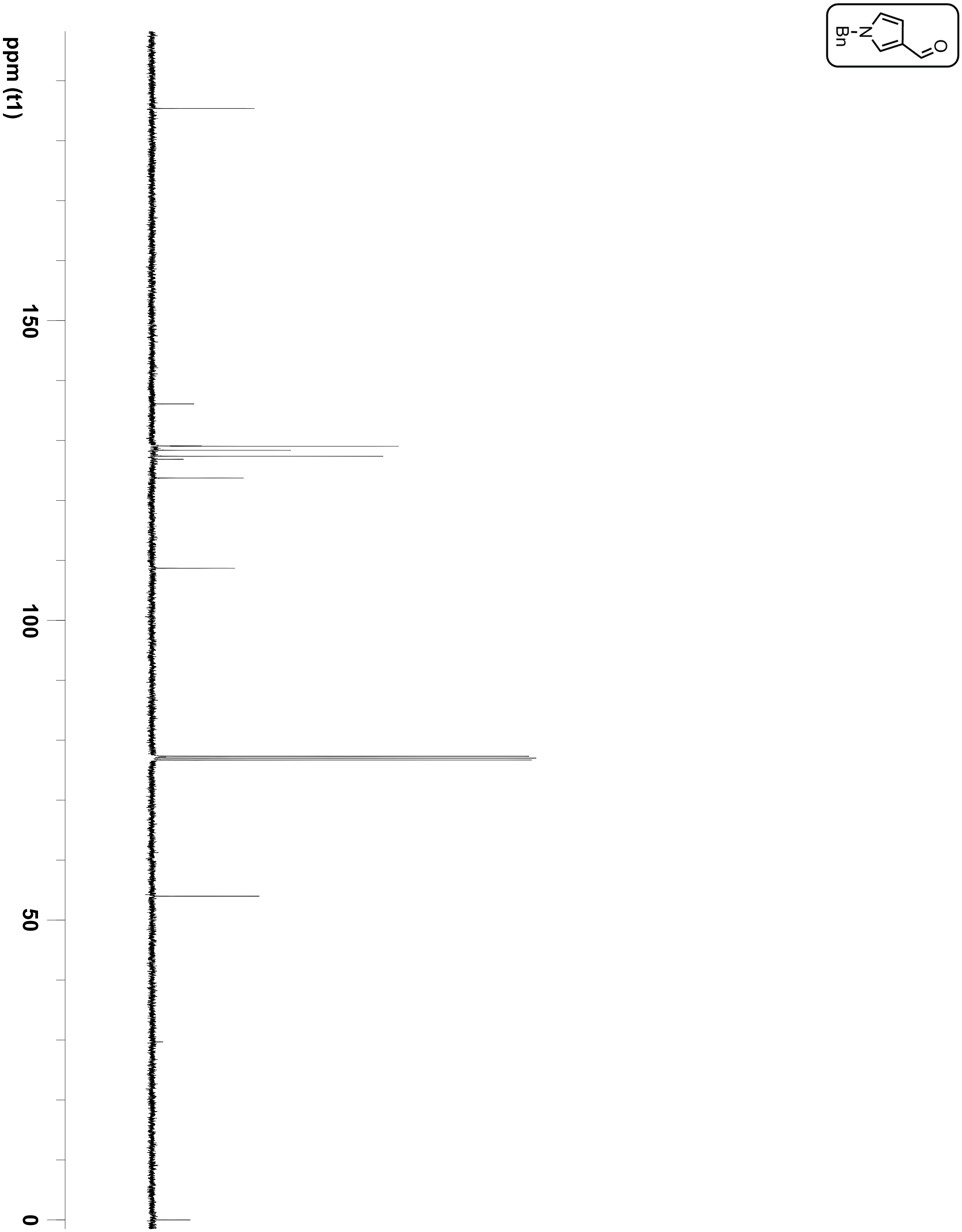

N
Bn
NO$_2$
ppm (f1)
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

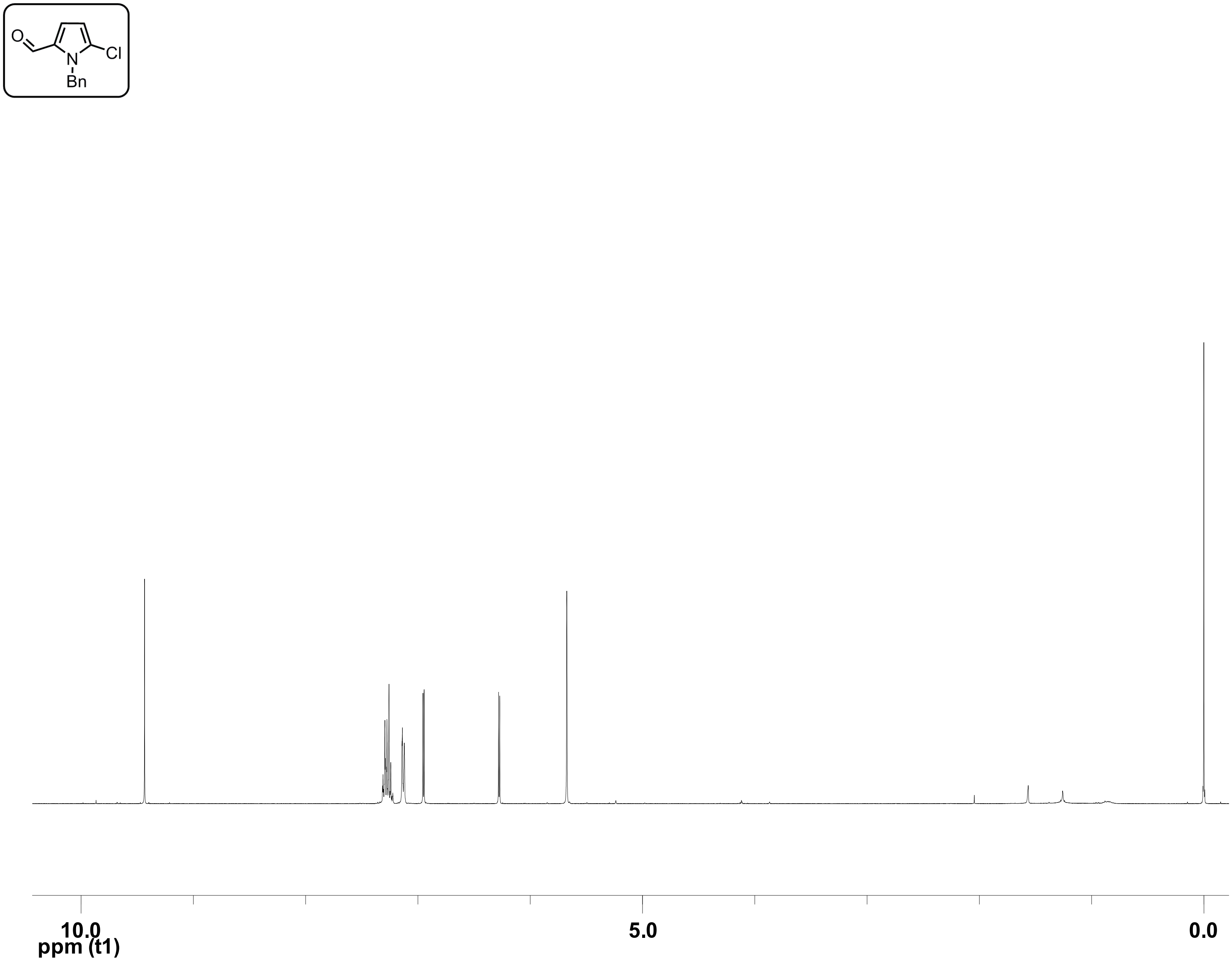

ppm (t1)
150
100
50
0
N
Bn
NO$_2$

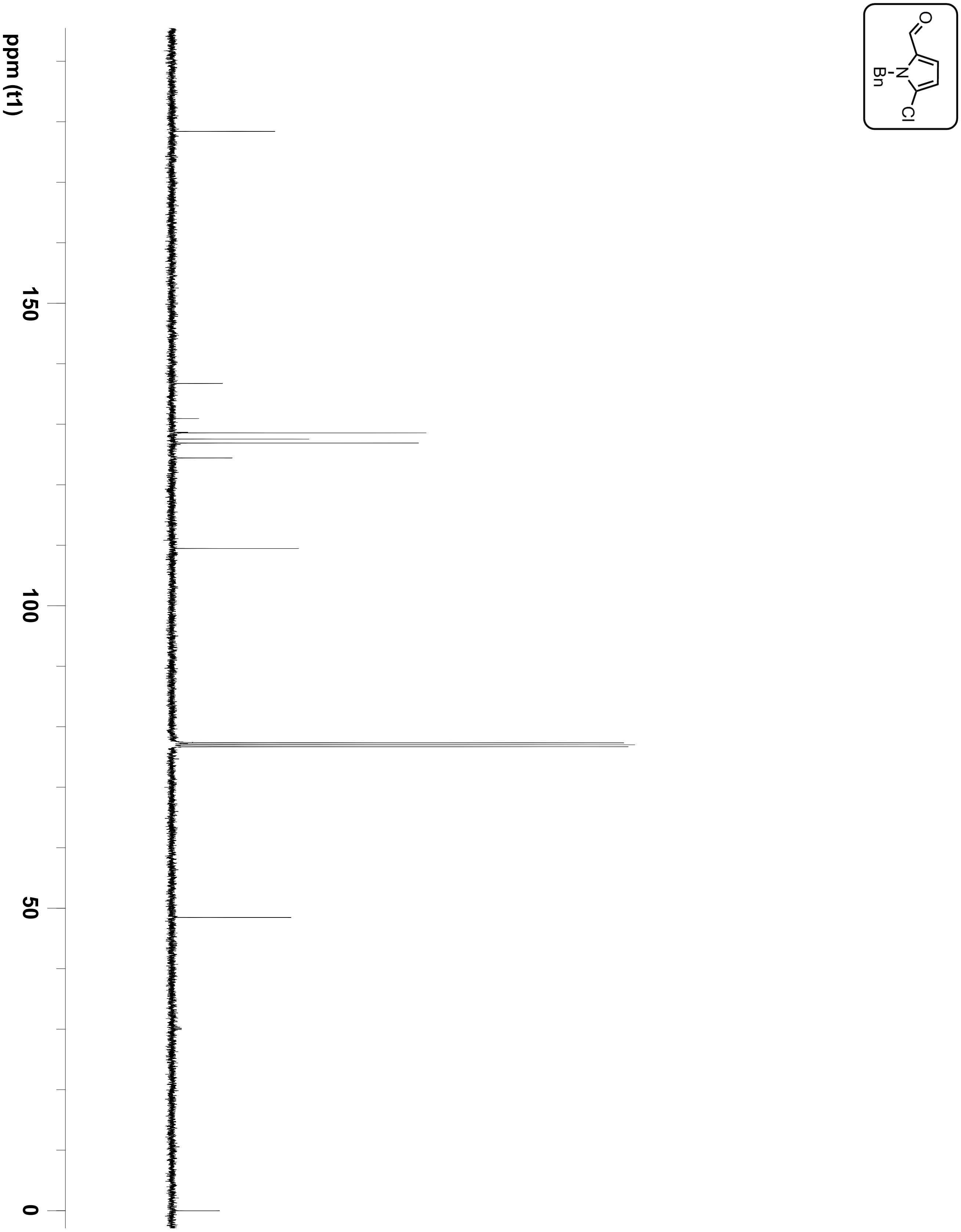
ppm (t1)
10.0
5.0
0.0
N
Bn
O

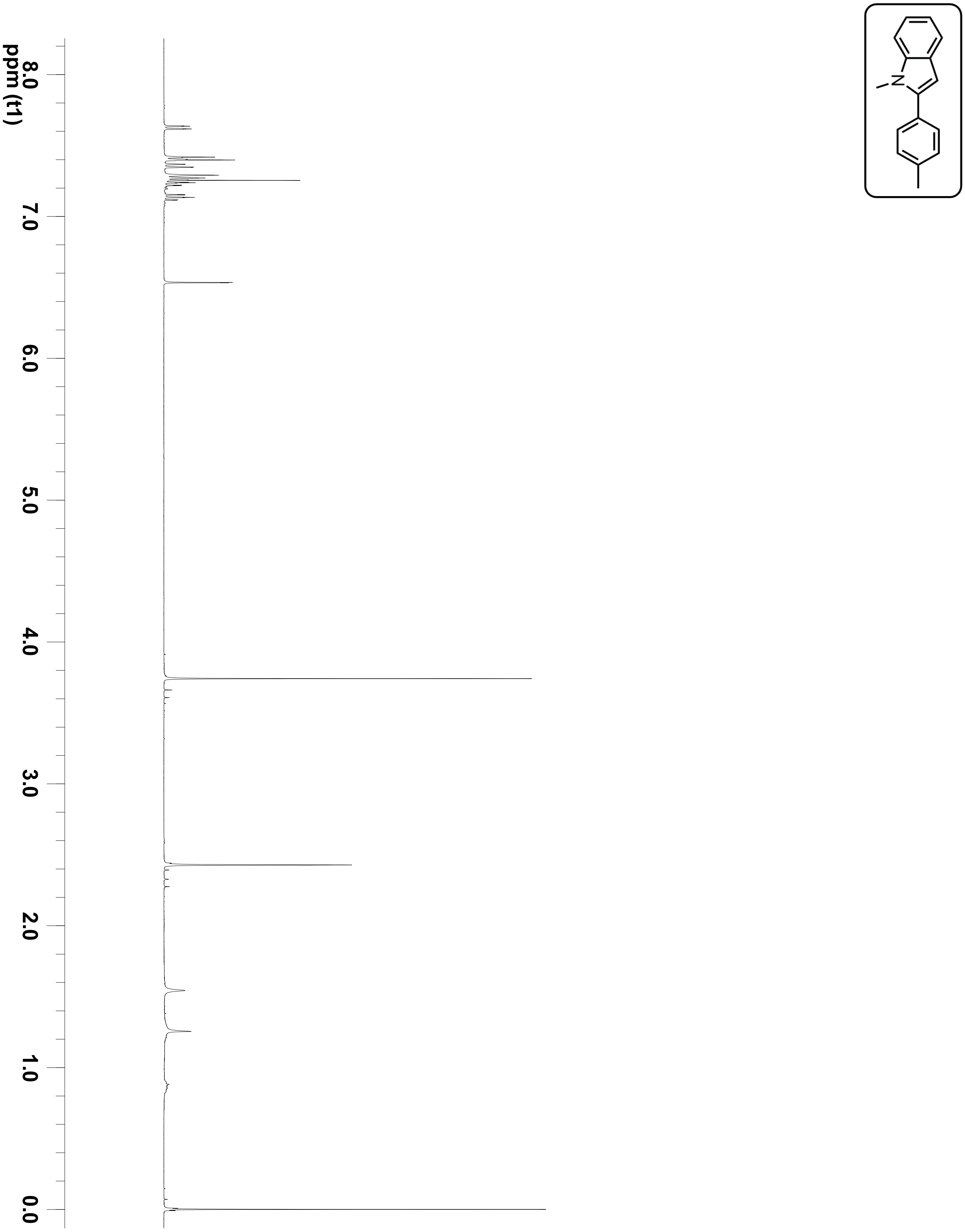

N
Bn
O
200
150
100
50
0
ppm (t1)


ppm (t1)
10.0
5.0
0.0
N
Bn
O

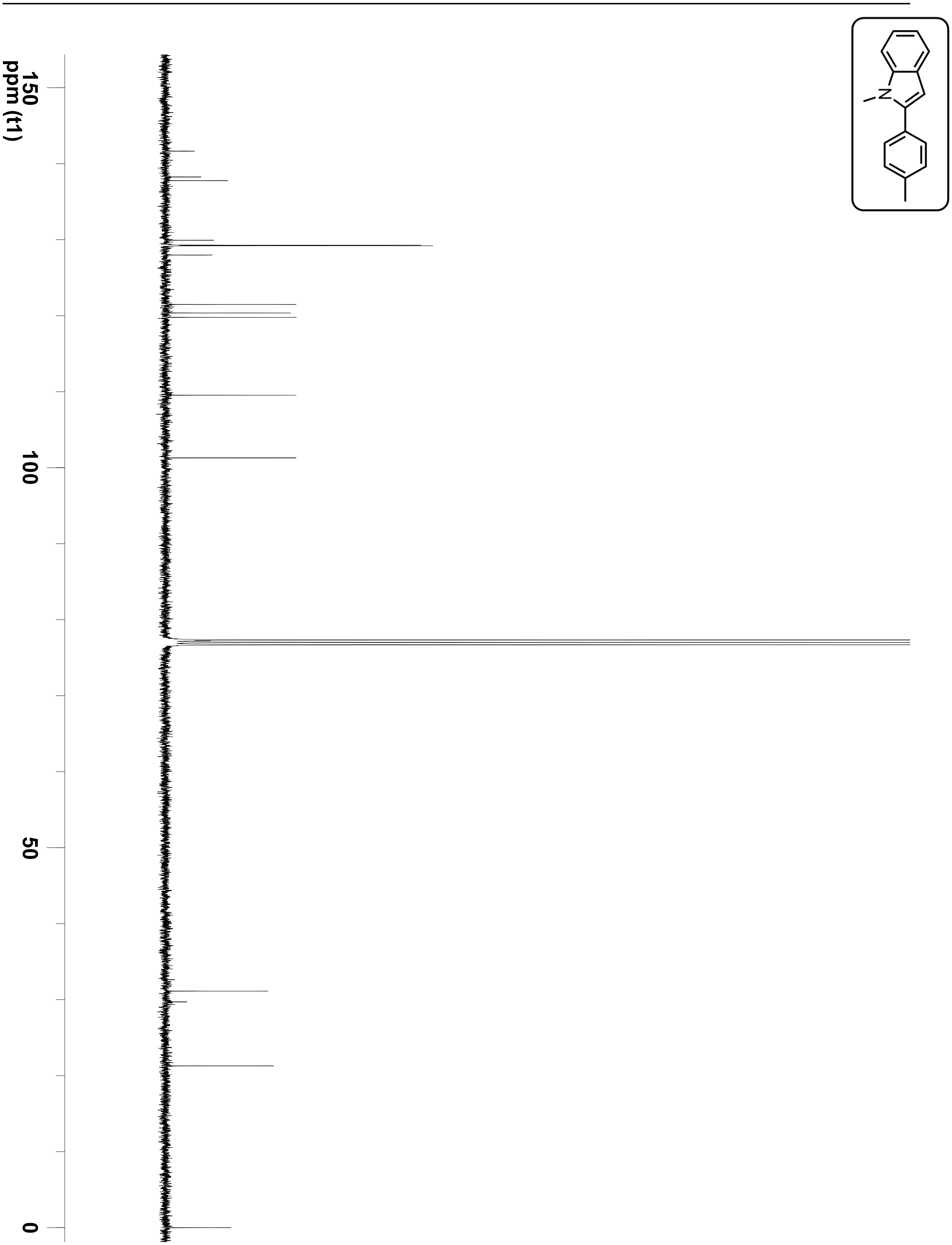

ppm (t1)
150
100
50
0
N
Bn
O

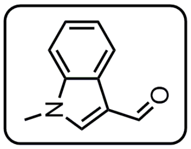

O
N
Bn
Cl
10.0
ppm (t1)
5.0
0.0

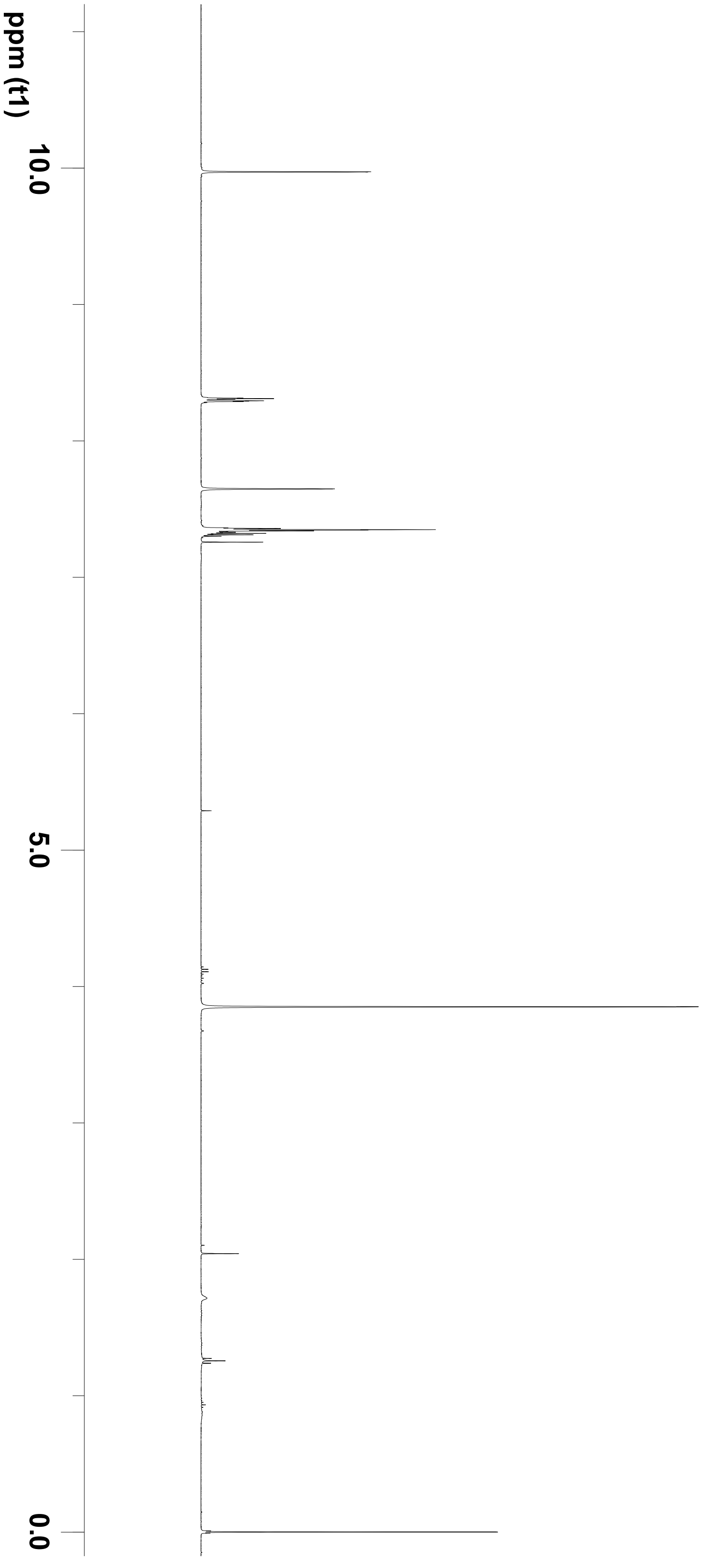

O
N
Bn
Cl
ppm (t1)
150
100
50
0

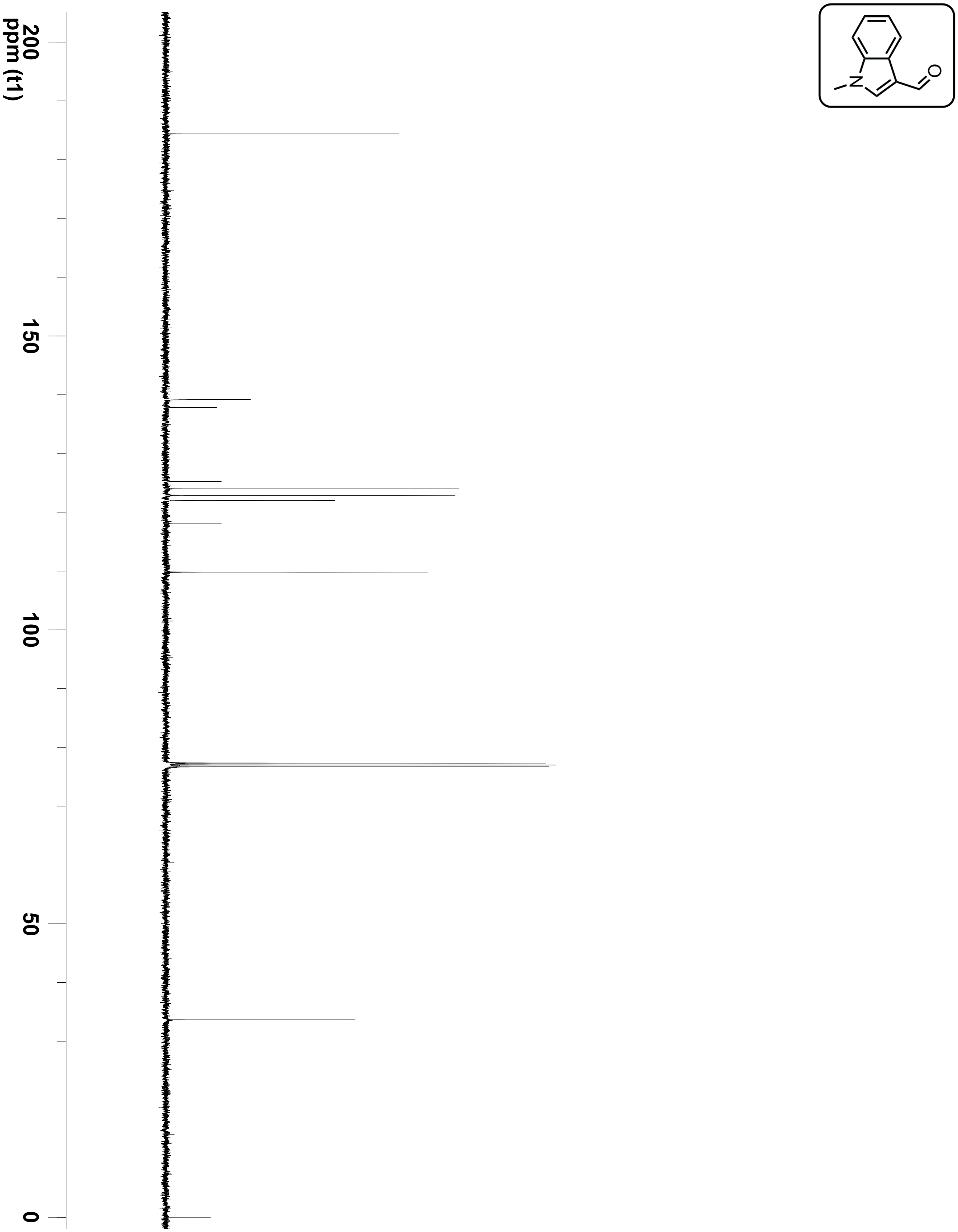


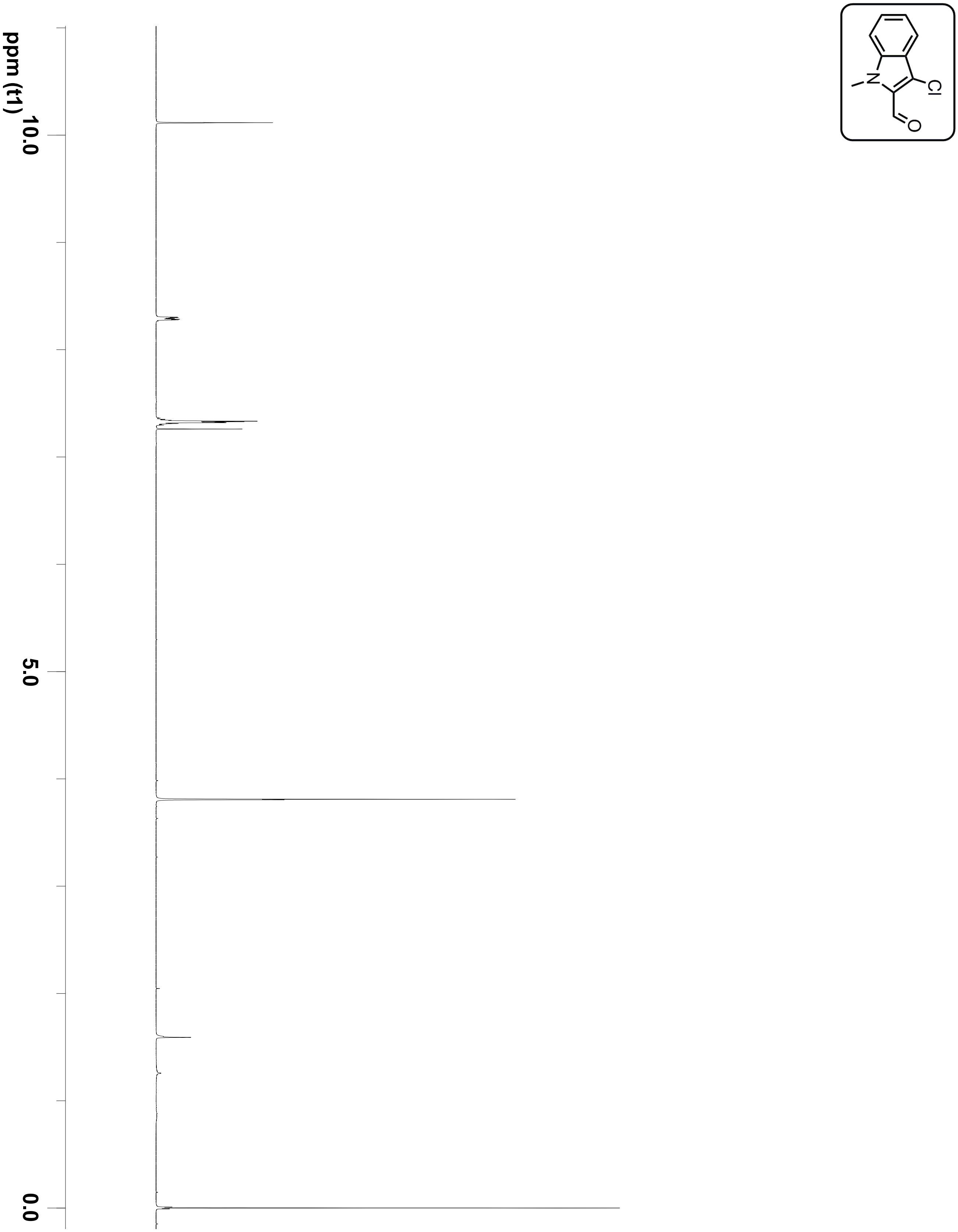
N
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

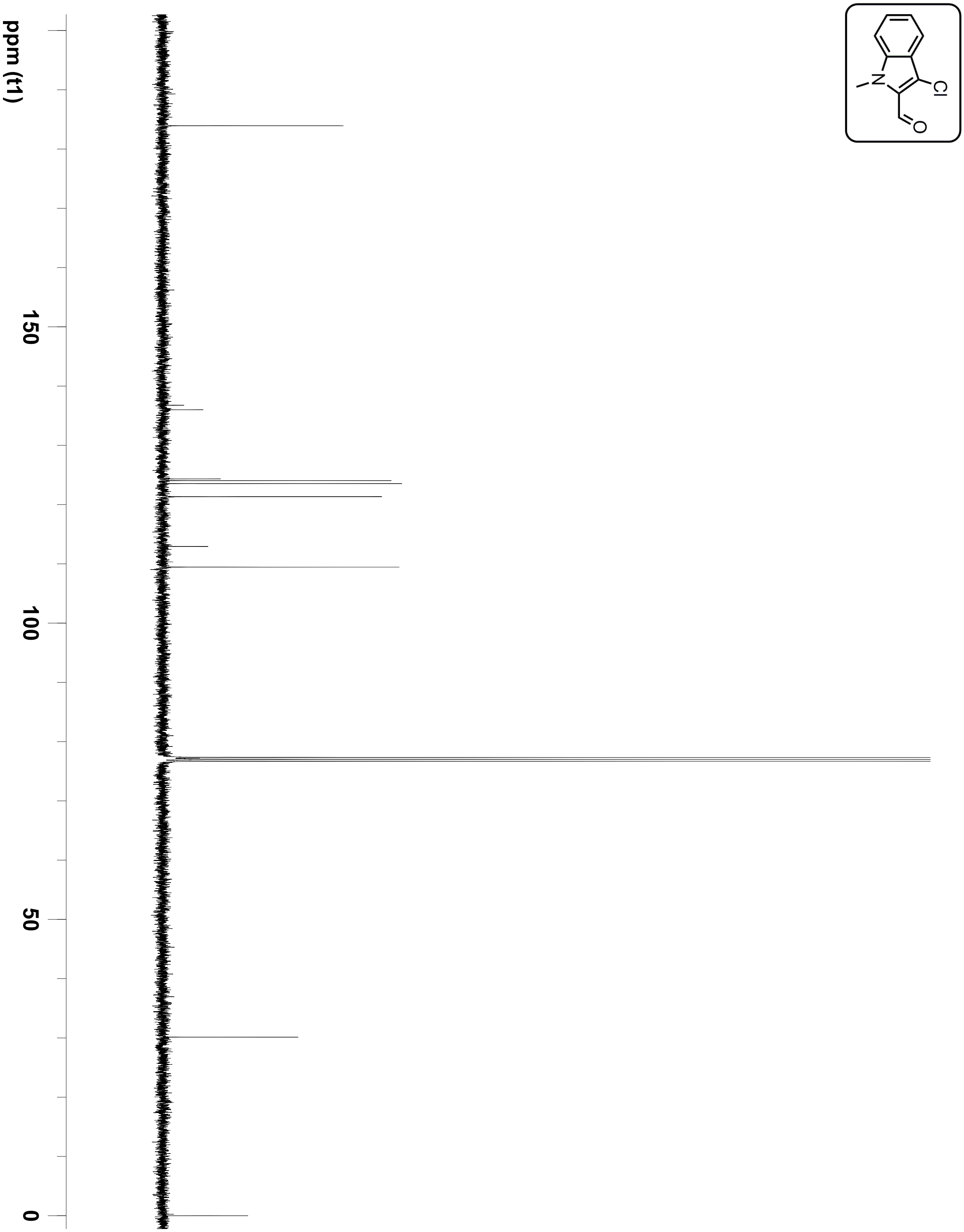

150
ppm (t1)
100
50
0
N

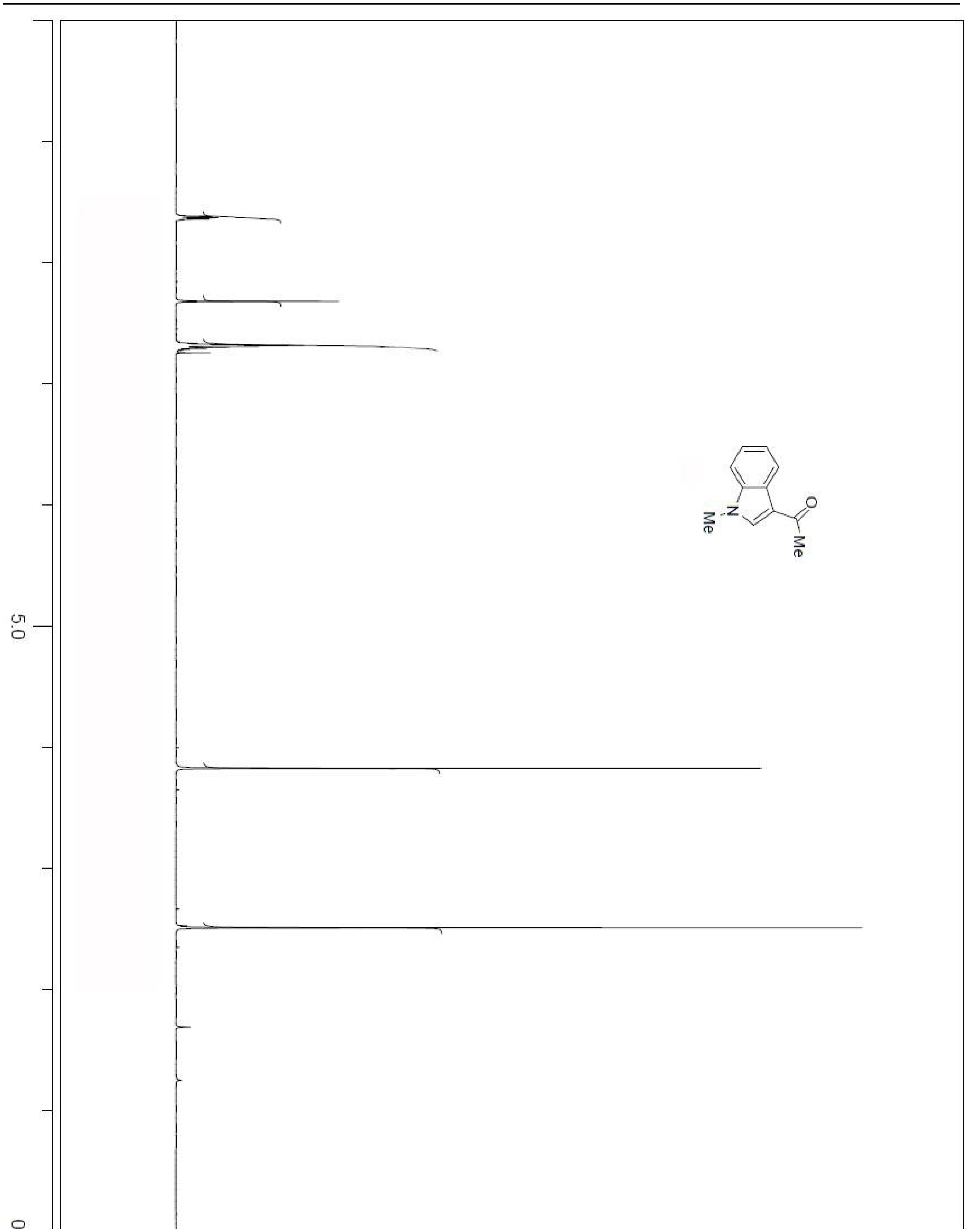

N
O

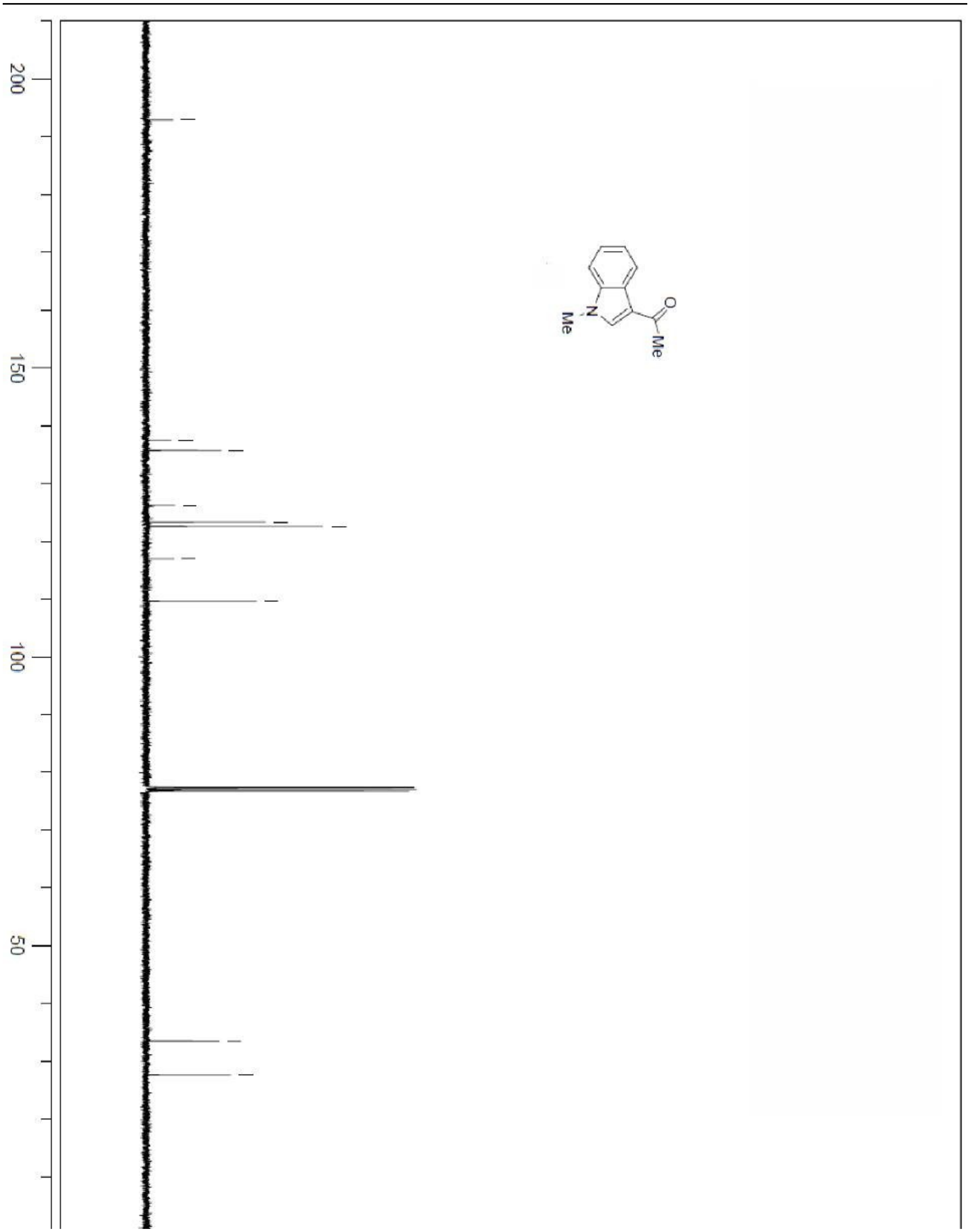

ppm (t1)
10.0
5.0
0.0

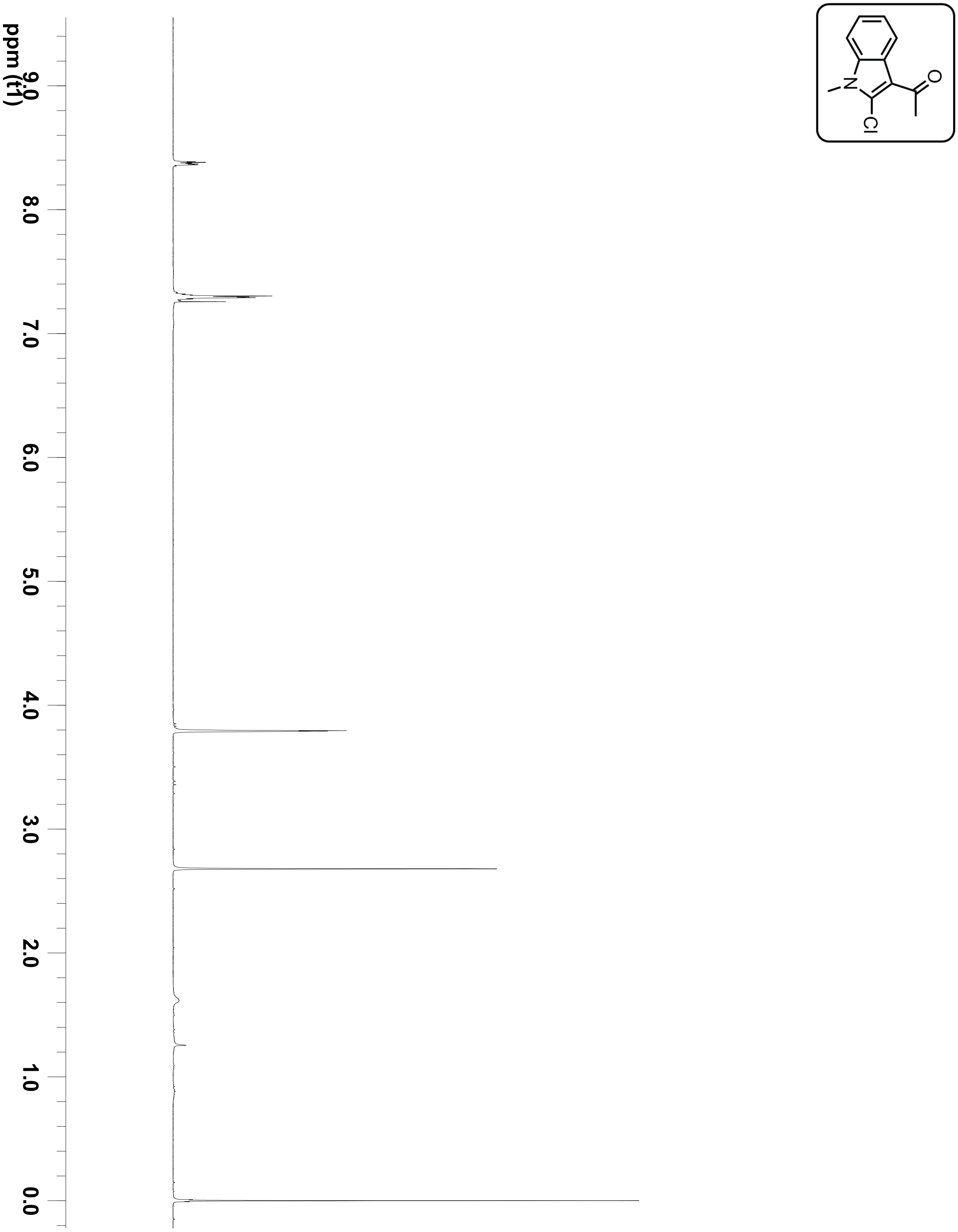

200
150
100
50
0
ppm (t1)
N
O

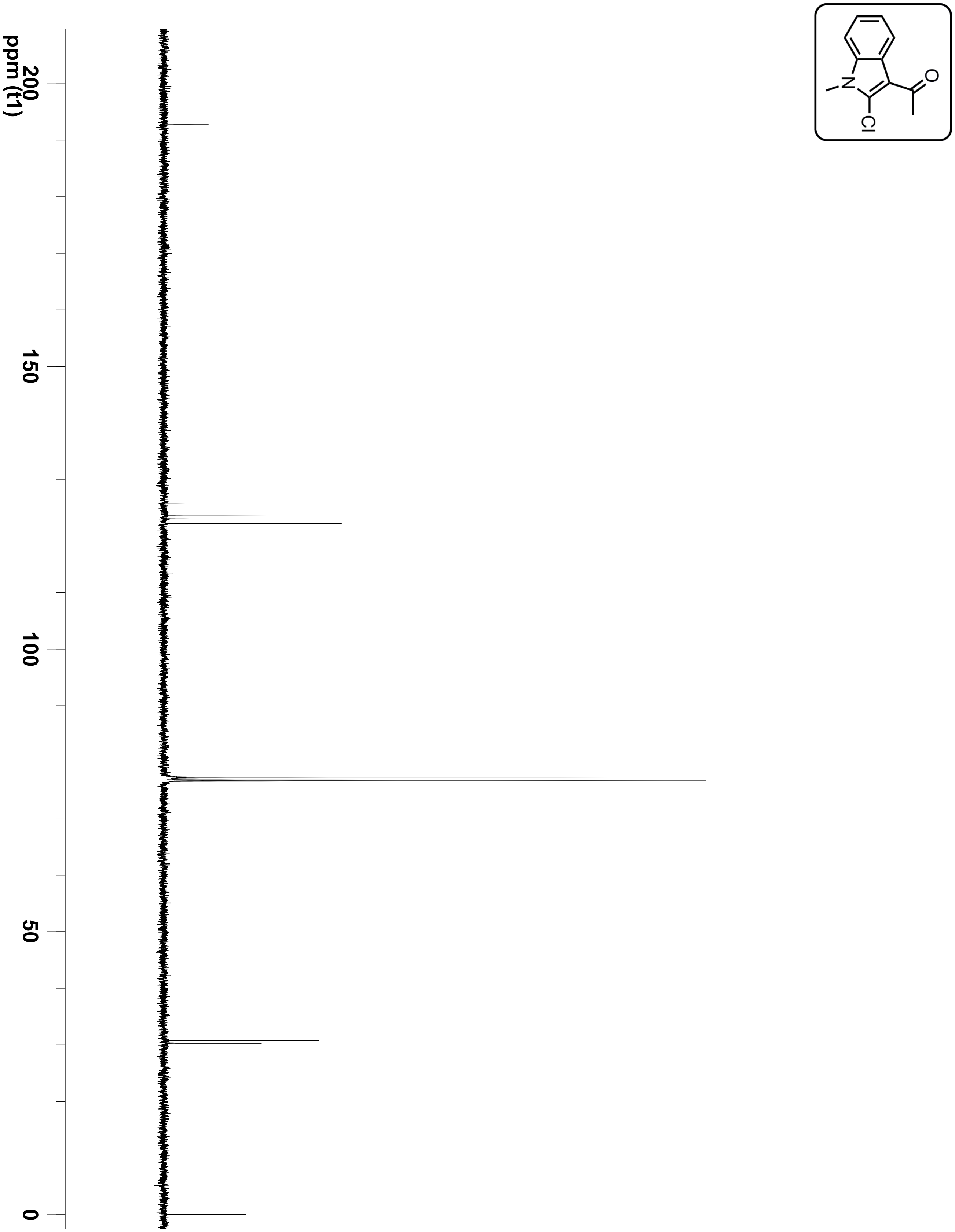

ppm (t1)
10.0
5.0
0.0
N
Cl
O


ppm (t1)
150
100
50
0
N
Cl
O


5.0
0
N
Me
O
Me


200
150
100
50
N
Me
O
Me


ppm (t1)
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
N
O
Cl


ppm (t1)
200
150
100
50
0
N
O
Cl